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MERCURIC BICHLORIDE POISONING*

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AS PART of a general review of cases of poisoning at the Boston City Hospital, 54 cases of mercuric bichloride poisoning from 1934 to 1946 were reviewed. In view of the recent introduction of specific therapy for mercury poisoning, it seems appropriate to present this series in order to re-emphasize the natural history of the results of mercury ingestion, as an aid in the evaluation of newer forms of treatment. In addition, the cases with renal damage in this series are worthy of attention in view of the current interest in the treatment of acute renal insufficiency.

Mercury poisoning may result from exposure to different forms of mercury, by varied routes and in both acute and chronic fashion, with accordingly different clinical manifestations.[1] Metallic mercury vapors have been reported as a cause of industrial poisoning. Among the inorganic mercurials, mercurous chloride (calomel) is used therapeutically, toxic effects resulting only when there is conversion to and absorption of the bivalent mercuric ion. Toxicity from the organic mercurials, that is, mercurial diuretics, is well recognized. The following discussion will deal with acute mercury poisoning resulting from the ingestion of the inorganic compound, mercuric bichloride (corrosive sublimate).

Mercuric bichloride is readily available to the public and is usually sold in ½-gm. tablets for use in disinfectant solutions. Warning of its poisonous possibilities is given by the distinctive blue coffin-shaped tablets in which form it is dispensed. An indication of its popularity as a means for attempting suicide is that it ranked sixth in a list of more than 25 of the commoner toxic ingestants at the Boston City Hospital from 1934 to 1943.[2] Reports of mercuric bichloride poisoning, with special reference to newer methods of treatment, continue to appear frequently.

From this thirteen-year period (1934–1946) there were available 65 cases diagnosed as mercuric bichloride ingestion. It became apparent on review of the records that only 54 cases were acceptable as true examples of corrosive-sublimate ingestion. The remainder of the cases either were misdiagnosed or yielded incomplete clinical records. There were 25 males and 29 females, ranging in age from 2 to 60 years. Suicidal intent was admitted by 44 patients. Fourteen patients were acutely alcoholic at the time of admission. As might be expected, the incidence of psychiatric disorders was high.[3]

Following the ingestion of mercuric bichloride, the patient may follow one of several clinical courses. A few cases are asymptomatic, whereas the majority develop gastrointestinal symptoms. Of the latter, some patients develop renal lesions that may terminate fatally. The initial, and frequently the sole, lesions are gastrointestinal. These may be sufficiently severe in a small number of cases to result in death in a few hours, or they may be relatively minor in nature. Those patients who develop renal involvement invariably have severe gastrointestinal symptoms (Table 1). In this series, 4 patients were asymptomatic and 32 patients developed gastrointestinal lesions only. These varied in degree from mild gastritis to a severe corrosive gastritis that terminated fatally in a few hours. The latter occurred in 1 patient. Eighteen patients developed evidence of renal disease with their gastrointestinal lesions. Nine of these 18 cases had a fatal outcome.

It is evident that the majority of patients suffer only initial damage to the alimentary canal. This is due to the direct corrosive effect of the ingested poison. The clinical picture in these patients is usually one of steady improvement following the first symptoms, since the damage, though rapidly effected, is primarily local, and healing is prompt. In none of these cases, nor in any of the reported series,[4-10] are there any instances of gastrointestinal sequelae.

The more important cases of mercury poisoning are those in which a renal lesion develops. In all cases

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this was evident on admission to the hospital. The patients who survived showed rapid clearing of the urine and no significant diminution of urinary output. The patients who died developed azotemia and anuria and died in from six to twenty-three days after ingesting the poison. The majority died within nine days. Among the fatal cases, the white-cell count was elevated in only 5, and there was a significant fall in the hemoglobin level in only 4. Anuria developed in from a few hours to three days after poisoning. Severe gastritis and colitis, manifested by grossly bloody vomiting and diarrhea, were prominent symptoms. Elevated temperatures were not found.

The dose of mercuric bichloride capable of producing death has been discussed by many authors.[11] It has been stated that ingestion of 1.5 gm. often led to a fatal termination. In this series the dose varied from less than 0.5 gm. to at least 4.0 gm., the smallest lethal dose being 2.0 gm. The smallest dose producing urinary changes was 0.33 gm.; the highest dose that did not produce urinary changes was 2.5 gm. However, in those patients who showed urinary changes the dosage was almost uni-

TABLE 1. *Résumé of Cases with Renal Involvement.*

Case No.	Age	Sex	Dose of Mercuric Bichloride	Hours before Admission	Signs and Symptoms	Blood Non-protein Nitrogen*	Urine Albumin*	Urinary Red-Cell Count*	Urinary White-Cell Count*	Treatment in Hospital	Course
			gm.			*gm./100 cc.*		*per high-power field*	*per high-power field*		
1	24	F	0.33	¾	Nausea, hematemesis, epigastric tenderness	23	+	0	10–25	NaFS,‡ gavage, parenteral fluids	Urinary output good. Recovery
2	45	M	0.5	5	Oral pain, nausea, hematemesis, oral-cavity burns	60	+	0–5	Loaded	NaFS, gavage, parenteral fluids, blood transfusion	Urinary output good. Recovery
3	27	F	0.5–1.0	—	Vomiting, epigastric pain and tenderness	34	+	Loaded	Loaded	NaFS, gavage, parenteral fluids	Urinary output good. Recovery
4	29	M	1.0	½	Nausea, vomiting, abdominal pain	29	+	0–5	Loaded	NaFS, gavage	Urinary output good. Recovery
5	34	F	1.0	1	Nausea, hematemesis, oral-cavity burns	—	+	50–100	0	NaFS, gavage, colonic irrigation, parenteral fluids	Urinary output good. Recovery
6	28	F	1.0	2/3	Nausea, vomiting, oral-cavity burns	31	+++	0	3–4	Gavage, parenteral fluids	Urinary output good. Recovery
7	47	M	1.5	1/3	Nausea, vomiting, oral pain	39	+	0	0	NaFS, gavage, colonic irrigation	Urinary output good. Recovery
8	37	F	4.0	1	Nausea, vomiting	32	+	10–15	0–5	NaFS, gavage, parenteral fluids	Urinary output good. Recovery
9	57	M	?	1	Nausea, hematemesis, abdominal pain, bloody diarrhea	62	+++	5–10	0	NaFS, gavage, parenteral fluids	Urinary output good. Recovery
10	34	F	2.0	3	Nausea, hematemesis, abdominal pain, oral-cavity burns	34–98†	+	0	0–5	NaFS, gavage, colonic irrigation, parenteral fluids (3 liters daily)	Anuria from second day. Died in pulmonary edema on eighth day
11	38	M	2.5	7	Hematemesis, bloody diarrhea, oral-cavity burns	48–137	—	—	—	NaFS, gavage, parenteral fluids (2 liters daily)	Anuria from admission. Died on eighth day
12	54	M	2.5	48	Nausea, hematemesis, bloody diarrhea, oral-cavity burns	87	—	Loaded	—	NaFS, parenteral fluids	"Few drops of bloody urine on day prior to admission," then anuria. Died on fourth hospital day
13	60	M	3.0	72	Abdominal pain, hematemesis, bloody diarrhea, oral-cavity burns	86–201	+	0–5	0–5	Parenteral fluids	Oliguria from first day. Died on twentieth hospital day
14	31	M	3.5	72	Severe vomiting, oral-cavity burns	100	—	—	—	Parenteral fluids	Anuria from admission. Died on third hospital day
15	33	M	3.5	24	Nausea, hematemesis, bloody diarrhea, abdominal pain	54–170	+	1–5	5–20	NaFS, parenteral fluids	Anuria from first day. Died on fourteenth day
16	27	M	"Many tablets"	1	Abdominal cramps, hematemesis, bloody diarrhea on second day	65–190	+	Loaded	Loaded	NaFS, gavage, parenteral fluids (2.5 liters daily), diathermy to kidneys	Anuria from first day; 60 cc. urine on fifth day and 300 cc. on sixth day. Died on sixth day
17	45	F	"Many tablets"	2	Abdominal pain, hematemesis	34–58	+	0–5	4–5	NaFS, gavage, colonic irrigation, parenteral fluids (3.0–4.0 liters daily)	Oliguria from third day. Died in pulmonary edema on sixth day
18	30	M	?	¾	Abdominal pain, hematemesis, bloody diarrhea on second day	120	+	0	0	NaFS, gavage, blood transfusions, parenteral fluids (3.0–4.0 liters daily)	Anuria from third day. Died on eighth day

*Findings on day of admission.
†Second value indicates subsequent rise.
‡NaFS = Sodium formaldehyde sulfoxalate given intravenously and by stomach tube.

formly higher when anuria was produced than when there was no change in urinary output. One would like to establish a definite correlation in man between dosage and mortality, as has been done in dogs.[12] It seems certain that this will not be possible because of the many variants that are introduced in human beings. Among the more obvious of these variants is the difficulty of determining the actual dose ingested and the amount retained.

The "emesis interval" has been defined as the time elapsing from ingestion to the first vomiting.[5] Much stress has been laid on the importance of this interval, which is supposed to modify the amount of poison retained and thus have a direct bearing on the prognosis. An emesis interval of fifteen minutes has been given as critical, with prognosis considered better if the interval is less.[12] In this series, as in others,[5, 9] no correlation was found between emesis interval and severity of poisoning. The interval was brief in the majority of cases. In practice, estimation of the emesis interval is usually difficult and appears to have no great prognostic importance in a given case of poisoning.

Because few patients in this series received treatment prior to hospitalization, it is impossible to evaluate its importance. It is significant, however, that the time before hospitalization was delayed in the majority of fatal cases. It was as much as twenty-four to forty-eight hours in 4 cases, whereas it was less than two hours in most of those that survived, both with and without renal involvement. This suggests that the treatment received after admission may have influenced the outcome. All the cases received gastric lavage after admission to the hospital. In all but a few, this was followed by the introduction of sodium formaldehyde sulfoxalate solution, which was also given intravenously. The other major aspect of therapy was the parenteral administration of fluids in all the fatal cases.

Much experimental work has been done on the pharmacology of mercury poisoning. It has been shown that about ten minutes is required for a tablet of mercuric bichloride to be absorbed from the stomach.[9] After absorption in the case of persons who die of poisoning, mercury has been shown in every tissue and fluid of the body. The greatest amounts are found in liver, kidney, blood and muscle.[6] In the rabbit, histologic changes in the kidney have been demonstrated as early as five minutes after ingestion of the poison[14]; marked lesions have been found one hour after injection of mercury compounds.[18] Excretion of the mercury begins soon after ingestion; the metal may be found in the urine within two hours. Excretion takes place through the large bowel, the kidney, the liver, the gastric mucosa, the salivary glands and to a small extent through the skin. The large bowel and salivary-gland excretion begins within six to twelve hours. (To show how small an amount of mercury can be detected, it has been recorded that it is commonly found in the urine of dentists and of people with amalgam tooth fillings.[6])

It is readily understood that ingested mercuric bichloride first exerts its effects on the gastrointestinal tract. Thus 13 cases had oral-cavity burns, with a higher incidence in the fatal cases. It has been suggested[16] that the presence of acute alcoholism increases the secretion of mucus in the stomach, with resultant protective coating of the mercuric bichloride tablet. This was thought to slow its absorption. Acute alcoholism was not present in the fatal cases. However, it is difficult to confirm this supposition because of other variables. The toxic action of mercury also manifests itself at the sites of elimination. As the mercury is excreted by the kidney, the renal effects become apparent. Six patients in this series manifested diarrhea after the first day. This is the effect of the secondary excretion of mercury by the large bowel.

Pathologic lesions in cases of mercuric bichloride poisoning have been described in the kidneys, gastrointestinal tract, lungs, liver and brain.[5] The significant lesions are in the kidneys and alimentary canal. In the latter the findings are not specific; they are merely the result of corrosion and necrosis of the epithelium. In the kidneys one finds a severe necrotizing nephrosis, with destruction of the proximal convoluted tubules.[17] Glomerular function appears to be affected little if at all.[7] The findings at post-mortem examination vary with the time of death. Patients dying within forty-eight hours after the ingestion of the poison show severe hemorrhagic necrosis of the upper gastrointestinal wall. Persons who die in from two to seven days after ingestion show a necrotizing nephrosis. In patients dying after seven days, one finds evidence of regeneration of the kidney lesion.[18]

A review of the literature[4-10] reveals that many factors have been pointed out as being of marked prognostic import. These include the dose (whether or not taken in solution, after a meal or with alcohol), the emesis interval and the severity of gastrointestinal symptoms. Time before hospitalization, fever, shock, leukocytosis, fall in hemoglobin, albuminuria, anuria and rising blood nonprotein nitrogen have also been cited. At the risk of oversimplification, it may be stated that, barring death within a few hours from shock (an infrequent occurrence), freedom from urinary findings for forty-eight hours ensures a good prognosis. Of the urinary findings, only the appearance of anuria has in the past usually signified a fatal outcome. With the present more rational therapeutic approach to this problem, this need not be an invariable result.

The treatment of mercuric bichloride ingestion may logically be divided into two phases: attempts to forestall the anticipated toxicity and procedures aimed at diminishing the results of damage inflicted. Historically,[19] many therapeutic regimens have been advocated with these goals in mind. Early emesis

and gastric lavage immediately suggest themselves as means of preventing absorption of the tablet. If it were possible to accomplish these measures with a minimum loss of time, they would obviously be beneficial. However, because of the very nature of the conditions under which mercury is most often ingested, this is not always feasible. Certain sulfur-containing compounds have been used, on the basis of their reaction with mercury, to form a nontoxic, readily excreted substance. Among these are hydrogen sulfide, calcium sulfide, sodium thiosulfate and sodium formaldehyde sulfoxalate.[20] With the possible exception of the last of these, there has been no convincing demonstration of their clinical efficacy. It would appear reasonable to continue the use of sodium formaldehyde sulfoxalate both intravenously and by gavage, because of the indeterminate reports. Even this therapeutic measure is thought by some to be dangerous if administered at too great an interval after the poisoning.[21] Although sodium formaldehyde sulfoxalate was a major therapeutic agent in the present series, no definite conclusion can be drawn concerning its value. Other mechanical measures have been employed to decrease the absorption and speed the elimination of mercury. Cecostomy, colonic irrigation and massive fluid therapy have been used without satisfactory results.[6] Once evidence of renal damage has appeared, renal decapsulation, forcing fluids and exsanguination transfusions have been tried in attempts to minimize the results of the kidney damage.[11] None of these methods have been shown to be specific or useful — and they may be harmful.

In recent years the development of British Anti-Lewisite (2,3-dimercaptopropanol) has supplied a specific means of reducing the toxicity of mercury as well as of other heavy metals. Its mode of action is to allow the mercury to combine with its sulfhydryl groups rather than with the sulfhydryl groups of the tissues and thus prevent disruption of the tissue enzyme systems. The metal-BAL complex is then excreted.[22] The effectiveness of BAL as protection against renal damage has been unequivocally shown in experimental animals when it is administered soon enough.[12] Therapy was progressively less effective with decreasing dosage of BAL or increasing delay before initiation of therapy. It even seems that to a certain extent BAL can reverse the damage inflicted on the enzyme systems by mercury.[23] The clinical reports[10, 24, 25] are striking, but the individual case must be considered in the light of the previously mentioned difficulty of establishing a dose-fatality ratio for mercury in man. To be effective, BAL must be administered as early as possible. A recommended dosage schedule is an initial dose of 5 mg. per kg. of body weight, to be followed in one to two hours by a dose of 2.5 mg. per kg. A second dose of 2.5 mg. per kg. should be administered two to four hours later; in severe cases a third dose of 2.5 mg. per kg. should be given within the first twelve hours. On the second day, two doses of 2.5 mg. per kg. should be used, and on the third day a single dose of 2.5 mg. per kg. is to be given.[22]

Once renal damage is established, therapy must be directed at the acute renal insufficiency that may ensue. Much attention has been given to the use of peritoneal lavage and the "artificial kidney."[11, 25-28] The natural progress of this tubular damage begins with the onset of regeneration on approximately the eighth day, with clinical recovery (if it occurs) from the ninth to the twelfth day.[27] Care must therefore be taken not to attribute all recoveries to these measures. Indeed, careful and critical evaluation of the individual case is necessary before these procedures may be undertaken. The present better understanding of the principles of fluid and electrolyte balance make it possible in many cases to treat the patient "conservatively." Some specific indication, such as hyperpotassemia, may make it evident that the mechanical clearing of the accumulated electrolytes and metabolites is lifesaving.

It is important to differentiate the early anuria due to inadequate circulating blood volume and the anuria due to renal tubular damage. At one time the forcing of fluids in such cases was almost a standard procedure, in attempts to "wash out the mercury" and to produce diuresis.[4] As early as 1918, however, it was realized that the promotion of diuresis by the forcing of fluids did not contribute materially to recovery in these cases.[29] More recently, stress has been placed on the actual harm done by this attempted therapy in addition to its futility.[30] Two (Cases 10 and 17) and probably four (Cases 16 and 18) of the cases in this series — as others reported in the literature[31] — showed clinical and post-mortem evidence of acute pulmonary edema. This was apparently a major factor in causing death. In one case (Case 16) urinary output had returned, and eventual complete return of renal function would probably have taken place, as pointed out above. It must be stressed that careful attention to fluid and electrolyte balance constitutes one of the most important aspects of the treatment of mercury toxicity. Little need be said here concerning the use of routine supportive measures.

There was a mortality of 18 per cent in this series — much the same as that reported in earlier series.[5, 7-9] With the application of present-day therapy, this should be materially diminished, as indeed it has been.[10] In summary, the essentials of treatment should consist of the following: the administration of an effective antidote (BAL) in adequate dosage as early as possible; prompt institution of general measures, including gavage; supportive therapy, with special attention to fluid balance.

Other measures aimed at mechanical treatment of the uremia require careful analysis of the indications and rigid supervision of the patient. In those few cases with initial shock, treatment of the peripheral vascular collapse is of prime importance.

Summary

The clinical picture produced by the ingestion of bichloride of mercury may be viewed from two aspects. The gastrointestinal lesions produced, as from the ingestion of any corrosive substance, may vary from a mild gastritis to a severe necrotizing ulceration of the mucosa. In addition, a significant number of these patients develop specific renal involvement. This may manifest itself by albuminuria alone or may progress to an anuric state and uremia.

Prognosis in the individual case is excellent if no urinary abnormalities are shown within twenty-four to forty-eight hours. If there is renal damage, the prognosis is excellent if urinary output remains good for three days. In the anuric patient, the outlook is much poorer. The immediate administration of BAL and prompt gastric lavage appear to be the best therapeutic measures for mercuric bichloride ingestion. Management of the patient with anuria is best carried out with careful planned parenteral therapy. In the individual case some form of dialysis might be indicated.

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THE ROLE OF ADRENAL STEROIDS IN INFECTION AND IMMUNITY*

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THE adrenal cortex has long been regarded as playing an important role in resistance to infectious disease, but the therapeutic potentialities of cortical hormones in infections have been under considerable question in patients other than those with Addison's disease. The recently demonstrated responses of patients with diverse inflammatory and neoplastic disorders to the administration of pituitary adrenocorticotrophic hormone (ACTH) or to cortisone[1-4] indicate that fundamental mechanisms of resistance in the host are affected by the hormones. Our interest has centered on some of these mechanisms, through studies of patients with acute infectious diseases in which the etiology, pathogenesis and immunologic responses could be evaluated. Some of these studies were carried out in patients with pneumonia who were treated with ACTH and without antibiotics.

Observations in Pneumonia[5, 6]

When ACTH was administered to patients with pneumococcal pneumonia, defervescence and relief from symptoms and signs of toxemia occurred promptly, but bacteremia, rusty sputum containing many pneumococci and signs of consolidation persisted for several days. In one instance extension of the lesion occurred while the patient was afebrile and asymptomatic; when administration of ACTH was discontinued, the symptoms returned and the patient developed empyema. In two other patients, ACTH appeared to have induced a crisis; a very brief period of intensification of symptoms and toxicity was followed by diaphoresis and rapid defervescence. Subsequent convalescence was uneventful save for the persistence of bacteremia in one patient for thirty-six hours after he had become afebrile and while he was entirely asymptomatic. Some of the metabolic changes observed in patients receiving ACTH, as well as the clinical sequence of events, suggested that the crisis of lobar pneumonia may be related to adrenocortical activation.

There was no evidence in these patients that the adrenal steroids§ exerted any bactericidal effect; antibodies appeared at the anticipated time, with no clear indication of acceleration of their release at the time ACTH was administered or of any delay in their appearance. In primary atypical pneumonia cold agglutinins appeared at the usual time and with no relation to the time of administration of ACTH. Exacerbation of symptoms following the withdrawal of ACTH was observed also in a patient with primary atypical pneumonia who was asymptomatic save for cough while she was receiving the hormone. Similar exacerbations following withdrawal of hormone have been noted in patients with pulmonary tuberculosis,[10, 11] in whom defervescence and relief from toxic symptoms, as well as apparent healing of tuberculous ulcerations, have sometimes occurred while they were receiving ACTH. The causative organisms in tuberculous patients, as in those with pneumonia, were not eliminated from the sputum during ACTH therapy. Exacerbations after withdrawal of the drug have also been observed in many other illnesses of which the etiology is more obscure.

Such observations suggest that the adrenocortical steroids alter the host's reaction to the illness and do not affect the etiologic agent. As a working hypothesis it is assumed that the same fundamental mechanism of action of the adrenal steroids is operative in infectious diseases and in the other disorders in which ACTH and cortisone have altered the clinical course of the disease. It is pertinent, therefore, to ask: How important are the adrenal steroids in resistance to infection? By what mechanisms do they act to bring about the effects that have been demonstrated? Of what therapeutic use may they be in the management of infectious diseases? Direct evidence on these points is scant, so it is necessary to review some of the literature on experimental studies for possible clues.

Effect of Adrenalectomy on Resistance to Infection

The importance of adrenal steroids in resistance to infection cannot be fully evaluated at this time. Arguments based on studies made in patients with Addison's disease and in adrenalectomized animals are not necessarily pertinent, but they are suggestive. Absence of the adrenal cortices renders the host extremely susceptible to a wide variety of chemical and physical injuries; adrenalectomized animals are much more susceptible than are intact animals to such commonly encountered agents as morphine, digitoxin, histamine, typhoidal vaccine, diphtherial toxin, foreign sera and many others. Adrenalectomized animals may succumb to in-

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§Only compound E (17-hydroxy-11-dehydrocorticosterone) and compound F (17-hydroxycorticosterone) are here referred to as adrenal steroids. There is evidence that other steroids are secreted by the adrenal cortex,[7-9] but only these two appear to be active in the treatment of rheumatoid arthritis.

fections that are adequately dealt with by intact controls; they also show increased susceptibility to anaphylaxis.[12-16] Adrenocortical extracts (ACE) restore the resistance of adrenalectomized animals to an approximation of the normal. It is of interest that not only cortisone but also some closely related steroids, which are inactive against rheumatoid arthritis, are effective in restoring resistance to bacterial vaccines.[17]

Very little is known of the comparative effects of different adrenocortical steroids. The capacity of such steroids to restore to an adrenalectomized animal the normal responsiveness to an infectious agent might make it possible to determine the specificity of adrenal steroids with respect to resistance to infection. Many of the metabolic and hematologic changes that follow injection of compounds E and F have been duplicated by the administration of steroids that are therapeutically ineffective in rheumatoid arthritis.[18-21]

Adrenalectomy probably does not affect the capacity to form antibodies, although some reports in the literature on this subject are confusing and contradictory.[15] Adrenalectomized animals that have been actively immunized to a toxic agent survive challenge doses many times greater than those that are fatal to unimmunized, adrenalectomized animals, so that active immunity is not greatly altered by adrenalectomy.[15] It has also been claimed by some workers,[22] and denied by others,[23] that adrenalectomized animals are incapable of the anamnestic response. Complement is not significantly lower in adrenalectomized animals than in controls,[15, 24] but the function of macrophages and of other phagocytic cells is distinctly impaired.[25]

It appears, then, that adrenalectomy reduces the innate capacity of animals to adjust the body economy to the presence of toxic materials, whereas acquired immunity may still be induced and retained.

Effect of Cortical Hormones on Resistance of Intact Animals to Infectious Diseases

When attempts are made to increase the resistance of intact animals, many more complicated factors are involved. Many of the earlier data are difficult to evaluate because of the problem of low and varying potency of cortical extracts. Furthermore, the administration of potent hormonal preparations is followed by various homeostatic adjustments. Thus the injection of adrenal steroids may depress pituitary function[26] and thereby also depress thyroid or gonadal function as well as other metabolic activities that may be critical to the mechanisms under study. Finally, it has been demonstrated that when an intact animal is undergoing some type of stress, the tissue need for cortical hormones and perhaps the rate of their utilization by the tissues are increased. This is presumably also true in infections, so that an adrenalectomized animal undergoing stress or infection must receive larger doses of the hormone to elicit a given response than a comparable animal not undergoing stress.[27] Studies in patients with pneumonia appear to be consistent with such an interpretation.[6]

Clinical studies dealing with the effects of ACE in infections have, on the whole, been rather poorly controlled. Even in such conditions as diphtheritic toxemia or the Waterhouse–Friderichsen syndrome there is considerable doubt that adrenal insufficiency is a primary cause of death and that adrenocortical extracts are actually of therapeutic value.[28-32] The experience with purified adrenocortical steroids has not been sufficient to make any judgment possible.

ACE, administered to intact experimental animals, has given slight but variable protection against diphtherial toxin; it exerts some protective effect against anaphylactic shock and against certain experimental infections in the guinea pig but has been found not to affect pneumococcal infections in the mouse, trypanosomal infection in the rat or anaphylactic shock in the dog.[33-36] Large doses of ACTH, in our studies, have failed to increase the resistance of mice to pneumococcal or influenza viral infections, nor have they interfered with the multiplication of the virus. The point should be made, at this time, that the dose of ACTH that is used in animal studies may be deceptively different from the dose that might be expected by analogy with man. In mice, using the circulating eosinophils and lymphocytes as indices, as much as 2.5 mg. of ACTH is necessary to produce greater depression of these counts than may be produced by handling the animals and injecting nonhormonal proteins.[37] ACTH has been found not to affect anaphylactic shock in the guinea pig, although it must be added that the proper dose of the hormone in these animals has not yet been ascertained.[38]

Some recent studies have indicated that ACTH and adrenocortical steroids play an important role in antibody formation.[39] Thus, higher titers of antibody have been demonstrated in animals immunized while receiving adrenocortical steroids than in animals not receiving such steroids. In hyperimmunized animals a single injection of ACE or ACTH induced within six hours an increase in the antibody titer, which reached its maximum level in nine hours and then slowly declined. These latter fluctuations were correlated with lysis and regeneration of lymphocytes in lymphopoietic organs and were also correlated with lymphocytopenia in the blood.[39] Because normal serum gamma globulin has been demonstrated to be associated with lymphocytes,[39, 40] the effect of ACTH and of cortical steroids on gamma-globulin levels in the blood plasma was studied; increases were observed in both gamma-globulin and antibody titers.[39] In addition, these studies showed that the anamnestic

response was stimulated by injection of adrenocortical steroids and was absent in adrenalectomized animals.[22]

Subsequent observers, however, have been unable to confirm some of these observations; most of the studies indicated that ACTH and cortisone have no effect on a wide variety of antibodies or that if there is an effect there is usually a slow decrease in antibodies in the plasma during treatment with steroids.[41-44] Similarly, gamma-globulin levels tend to decrease during administration of cortical steroids.[2, 3] Stimulation of acquired immunity by the use of cortical extracts could not be demonstrated,[42] and the anamnestic response has been described as unrelated to adrenocortical function by some[23] and as stimulated by adrenal cortical steroids by others.[39, 45] The experimental details cannot be discussed at this time, but most of the evidence suggests that ACTH and cortisone have little effect on antibody formation, save in diminishing the over-all antibody and gamma-globulin contents of the blood during prolonged administration of the hormones. The reason for the discrepancies among observed results remains to be clarified.

Role of Adrenocortical Insufficiency in Infection

In many of the diseases in which ACTH and cortisone exert clinical effects, adrenocortical insufficiency cannot be demonstrated and is probably not a primary pathogenetic factor.[9] In acute infectious diseases, however, autopsy evidence suggests that some degree of adrenal depletion may be present in fatal cases.[46-48] In some instances, such as in diphtheritic, meningococcal and other severe toxemias, frank necrosis of the adrenal glands, with many mitoses in the surviving cortical cells, has been frequently observed.[49] On the other hand, histologic evidence has been found of adrenocortical hyperactivity in experimental animals; it has occasionally been shown in man when death occurred shortly after recovery or after the most acute phase of the disease had subsided.[48, 50]

It is not known whether the apparent adrenocortical insufficiency seen in some cases is due primarily to direct attack upon the adrenal cortex or to effects exerted upon the hypothalamic nuclei[51] or the hypophysis and thence upon the adrenal cortex.

Physiologic Effects of Adrenal Cortical Activation in Infection

The data on this score are scattered and incomplete. Some pertinent observations may be mentioned.

Fever. Fever, the most commonly used index of the presence of infection, is attenuated by ACTH and cortisone,[52, 53] but the role of this antipyretic action in clinical defervescence can only be surmised.

Toxemia. It would be important to know if ACTH attenuates the direct toxic actions of infectious agents. Mice receiving ACTH are not protected against purified influenza virus, rickettsiae or *Salmonella typhosa* endotoxin administered intravenously in amounts that will cause acute toxic death.[54, 55] The attenuation of diphtheritic toxemia by ACE has been mentioned.

Cellular Permeability. It has been suggested that adrenal steroids alter cellular permeability.[56] Menkin has demonstrated that the increase in cellular permeability that is induced by substances in inflammatory exudate can be reduced by the administration of adrenocortical extracts.[57] Similar reduction of permeability is suggested by the lack of inflammatory exudate in wounds made in animals receiving ACTH or cortisone.[58]

The action of hyaluronidase in increasing permeability of connective tissue to dyes is reversed by the administration of ACTH and cortisone.[59] However, the role of hyaluronidase in resistance to infection is still not clear. The correlation between the occurrence of virulent micro-organisms and their production of hyaluronidase is not striking[60] and although hyaluronidase will in some instances increase the virulence of certain bacteria[61] it will protect against infection in others.[62] The occurrence of hyaluronic acid as a ubiquitous component of connective tissue and the almost equally wide occurrence of hyaluronidase in mammalian tissues suggest that the connective-tissue reactions in disease might conceivably be affected by adrenocortical steroids. In this connection, the evidence that fibroblastic regeneration (as in wound healing) is inhibited by the adrenal steroids is pertinent.[58, 63] It is still not clear, however, whether adrenal hormones directly affect connective-tissue metabolism or influence fibroblastic growth by secondary effects, such as the excessive nitrogen loss that commonly accompanies the administration of large doses of cortical hormones or ACTH.[2, 3]

Ascorbic Acid. The decrease in adrenal ascorbic acid in response to stress or to an injection of ACTH is a reliable index of adrenocortical activity.[9] In addition, there are many clinical indications of the interrelation of ascorbic acid and adrenocortical function. Thus, scurvy and adrenocortical insufficiency have some clinical similarities. Scorbutic patients are unusually susceptible to stressful situations. Blood levels of ascorbic acid are generally diminished in patients with infections, burns or similar traumas.[9, 64] On the other hand, scorbutic patients excrete normal amounts of corticoids[65] and have normal responses of circulating eosinophils to ACTH.[66] The evidence suggests that ascorbic acid may be important to the synthesis of steroids, but alternative substances may replace the vitamin in the synthesis of the hormones.[9] Although large doses of ascorbic acid have been used in the treatment of some rheumatic disorders, their effectiveness is still not generally accepted. Ascorbic acid given to normal persons in this laboratory has not

altered the eosinophil counts, even after administration of 5 gm. of ascorbic acid daily for two weeks.

Hypersensitivity

It has been observed that ACTH and cortisone sometimes abolish or diminish the intensity of skin reactions of the delayed tuberculin type, without affecting the immediate or anaphylactoid type of reaction.[67] It has, therefore, been suggested that one effect of the adrenal steroids is to dissociate the hypersensitivity aspects of a given illness from other phases of the disease. However, nonspecific irritants administered in the same fashion as tuberculin or other slowly acting specific skin antigens also elicit no inflammatory response if ACTH or cortisone is administered.[68] It is more likely that instead of interfering with antigen-antibody combination or with specific responses to sensitivity reactions, ACTH or cortisone acts to alter the capacity of the host's tissues to respond to certain types of irritants, irrespective of the involvement of specific immune mechanisms. The evidence that the Shwartzman reaction is attenuated by ACTH is also interpretable in this light.[69] The reaction of the skin to histamine and the acute anaphylactoid cutaneous responses, such as are encountered in certain allergic sensitivities or in the Arthus phenomenon,[70] are not affected by the hormones.

Metabolic Studies

Finally, there is evidence from our metabolic studies of patients with acute infectious disease that the pattern of excretion of sodium, potassium, chloride, uric acid, creatinine and phosphorus in such patients is similar to the pattern that is observed when normal persons are given ACTH. Furthermore, administering ACTH to such acutely ill patients merely accentuated some of the changes but did not alter the basic pattern. In addition, no one of the patients so far studied has shown any circulating eosinophils, on direct count at the height of his acute illness, before ACTH was given. The few observations that excretion of corticosteroids is generally increased in acute illness[71, 72] indicate that adrenocortical activation plays some role, as yet not clearly defined, in the physiologic response to infection. That these effects of adrenal steroids are not the sole determining factors in the physiologic response is indicated by the fact that bacteria and viruses have toxic effects on tissues by direct interference with tissue metabolism, and that not all of the physiologic disturbances induced by experimentally produced toxemia may be reversed by the administration of large amounts of cortical extract.[73] It is of interest that some of the metabolic changes observed following the administration of ACTH and cortisone have been shown to depend on alterations in renal function induced by the hormones,[74, 75] suggesting that similar changes in renal function may occur in acute infectious disease.

In summary, it is apparent that we have inadequate knowledge of the effects of these potent hormones. Each use of cortisone or ACTH should therefore be designed to add to existing knowledge. The evidence indicates that adrenal cortical activation commonly occurs in infectious disease, so there would be little need, ordinarily, to use adrenal hormones. Furthermore, the clinical effectiveness of adrenal hormones in the treatment of infectious disease is not well established. When adrenal hormones are considered for the treatment of acute infections, it should be with the clear understanding that unless there is evidence of adrenocortical insufficiency the hormones will at best act to restore a semblance of clinical recovery. They will not affect the etiologic agent, and unless other mechanisms are operative that will limit the duration of the disease the symptoms will probably flare up again and perhaps spread, after cessation of hormonal therapy. Evidence that adrenocortical insufficiency occurs in infectious diseases is fragmentary and inconclusive.

In no case can hormonal therapy, at least as now understood, be considered a substitute for specific chemotherapy. In no case should it be expected to do more than suppress the host's clinical response to the infection. Whether or not the ultimate resistance of the host to the offending agent is thereby increased is not clear.

The undesirable effects of the administration of ACTH and cortisone in the amounts needed to produce significant effects in patients with infections must also be borne in mind. These include: water retention and secondary effects on cardiovascular function, abnormal carbohydrate and increased nitrogen metabolism, nervous and mental reactions, skin manifestations, symptoms of Cushing's syndrome and others.

It must, therefore, be concluded that ACTH and cortisone have supplied potent tools for investigations of physiologic mechanisms but are not yet ready for general clinical use in patients with infectious diseases.

ADDENDUM

Since this review was written, many papers have appeared that deal with the effects of ACTH and cortisone on infection and immunity. Some of the pertinent ones will be summarized briefly.

The effects of ACTH and cortisone have been investigated in a variety of infections in human beings and in experimental animals. ACTH did not decrease the mortality of mice infected with pneumococci[76] or streptococci,[77] although treated mice frequently survived for a few hours longer than untreated controls.[76] ACTH did not significantly alter the course of pneumococcal infection in rats[77] nor of influenza A infections in mice or ferrets.[76, 78] The rate of multiplication of the virus in the experimental animals was not affected. Infection with

the virus of poliomyelitis was not affected by ACTH in hamsters and in mice;[79, 80] similar results were obtained with the virus of equine encephalomyelitis in mice.[80] In a carefully controlled clinical study, poliomyelitis was not affected by ACTH.[81] Cortisone has produced rapid clinical improvement in typhoid fever[82] and has increased the rate of recovery when given with chloramphenicol.[83]

On the other hand, there are indications that cortisone and perhaps ACTH may actually depress resistance to infection. Thus, cortisone increased the susceptibility of mice to pneumococcal and influenza A infections,[76] of rabbits to streptococcal infections,[84] of mice,[85] rats[86] and guinea pigs[87] to tuberculosis and of hamsters to experimental poliomyelitis.[79] Syphilomas produced in rabbits under treatment with ACTH or cortisone contained unusually large numbers of treponemes, and changes in the local lesions were described.[88] The skin lesions of North American blastomycosis were markedly aggravated by treatment with ACTH.[89] Polyarthritis induced by pleuropneumonia-like organisms in rats was not reduced by cortisone given either at the time of inoculation of the organisms or after the arthritis had been established.[90] Adrenal cortical extracts, however, when given to mice that had been partially protected by the administration of sulfadiazine or pantoyltauryl analogues, prolonged the life of the animals without decreasing the mortality rate.[91] Cortisone markedly inhibits the growth of chick embryos,[92] but the concentration of the viruses of influenza and mumps in embryonated eggs was greater in the presence of cortisone than in control embryos.[93]

When cortisone was administered to rabbits during the course of immunization, the depression of antibody formation that resulted was much greater than that occurring during the administration of ACTH.[94] Cortisone and ACTH increased the local susceptibility of skin to the hemorrhage that is induced by a single injection of meningococcal toxin.[95]

The evidence suggests that ACTH and cortisone may at times depress certain aspects of resistance to infection but that ACTH and adrenocortical extracts may at times prolong slightly the life of infected experimental animals without altering the final mortality rate. Cortisone, on the other hand, seems to depress resistance to infection more markedly than ACTH or adrenocortical extracts. The reason for this greater effect is not clear. It may merely represent fortuitous species differences in responsiveness to ACTH or cortisone. Thus, mice are unusually resistant to the effects of ACTH and in these animals cortisone produces more profound eosinopenia than an equal weight of ACTH.[76] This is in contrast to the experience in human patients, in whom ACTH may be many times more effective on a weight basis than cortisone. Another possible explanation for the difference in the effects of ACTH and cortisone is that the hormones secreted by the adrenal cortex have less depressant effects on immune responses than does cortisone, which is produced in small amounts if at all by the adrenal cortex.

In some clinical conditions such stimuli as mild intercurrent infection, chilling, exertion and so forth may precipitate acute exacerbations of preexisting illnesses or may increase susceptibility to others. Because such predisposing factors probably induce adrenocortical stimulation, it has been suggested that adrenocortical hormones may be of pathogenetic importance in some diseases.[96] Thus, ACTH administered to patients with induced benign tertian malaria caused significantly increased parasite counts in the peripheral blood. Similarly, ACTH given to monkeys with malaria due to *Plasmodium knowlesi* (which is similar to infection with *P. falciparum* in man) led uniformly to the production of blackwater fever, a hitherto unexplained complication. Crises have also been induced during the course of sickle-cell anemia by administering ACTH.[96]

Additional observations have also been reported that further support the concept advanced earlier in this paper that ACTH and cortisone act not on antigen-antibody unions nor on specific hypersensitivity mechanisms, but rather on certain components of the inflammatory response, whether or not the inflammatory agents are immunologically active. Thus, the passive Arthus phenomenon was not inhibited by ACTH or cortisone, and the active phenomenon was inhibited only if antibody formation was depressed by the hormones.[94] The local acute reactions to injected allergens in allergic individuals were not altered by ACTH despite symptomatic relief induced by the hormone.[97] Thus, despite the many publications indicating that various hypersensitivity reactions are inhibited by ACTH or cortisone,[67, 98-101] the common denominator appears to be that inflammatory reactions induced by such diverse stimuli as burns, turpentine, glycerol, jequirity, tubercle bacilli, trauma, mustard oil, formaldehyde, antigen-antibody reactions and probably other irritants are attenuated or inhibited by the action of the hormones.[62, 68, 87, 102-109] The inconstancy with which the tuberculin reaction has been inhibited may be due in part to differences in the dosages used. The uncommonly high requirements for ACTH and cortisone in certain experimental animals have not yet become universally appreciated.

It appears also that those immediate immune reactions in which the release of histamine plays an important role,[110, 111] such as anaphylaxis in the guinea pig[88, 101, 112, 113] and the Arthus phenomenon in the rabbit,[70, 94] are not affected by ACTH or cortisone, whereas the nonhistaminic and delayed types of reaction in which cellular infiltration and proliferation are more directly concerned may be inhibited by the hormones.[114, 115] On the other

hand, experimental nephritis, induced by cytotoxic serums, was not affected by ACTH or cortisone.[116, 117] Just which components of the inflammatory response are affected is not quite clear, but vascular changes, suppression of leukocytic infiltration, differences in the numbers of macrophages and inhibition of connective-tissue formation without effect on epithelialization have been described.[63, 68, 87, 102, 105-109, 118, 119]

Peritonitis has been reported in patients receiving ACTH.[120] This complication was presumably due to activation of peptic ulcers or of ulcerations of the colon.[121-122] This is an additional reason for caution in the use of these potent therapeutic agents.

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EXTRACT OF LICORICE FOR THE TREATMENT OF ADDISON'S DISEASE*

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EXTRACT of licorice has been in use in Western Europe for many years as an adjuvant for disguising the taste of other drugs in medical mixtures. It is also used in various forms as a sweet for children. In 1946, Revers[1] investigated its usefulness in peptic ulcer. He noted a beneficial effect in gastric ulcer, whereas in duodenal ulcer the effect was doubtful. Apart from this curative action on ulcer of the stomach (which may be due to the presence of a spasmolytic principle[2]), Revers[3] noticed that about 20 per cent of his cases developed edema and hypertension or cardiac asthma, or both. His observations have been confirmed by many physicians in the Netherlands, including ourselves. It was evident that these side-effects could not be due to damage to the heart or to the kidneys; the electrocardiogram remained normal, there were no changes in the urine and there was no diminu-

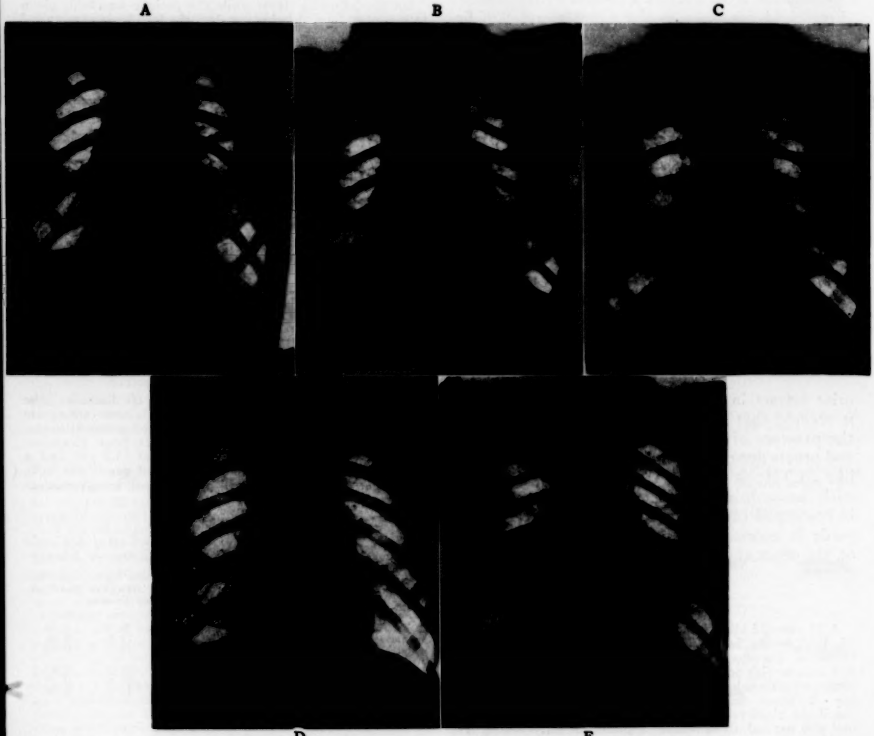

FIGURE 1. *Roentgenograms of Changes in Size of Heart.*
A = *Before treatment (August 17).* B = *After eight days' treatment with DOCA (September 11).* C = *After eight days' treatment with licorice extract (October 10).* D = *After seven days' withdrawal of licorice extract (October 16).* E = *After seven days of renewed administration of licorice extract (October 23).*

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tion in the protein content of the serum. Borst[4] and his co-workers[5] demonstrated that extract of licorice causes sodium retention and potassium loss, which leads to an increase in extracellular fluid and plasma volume and through this to an increased venous pressure with increase in systolic arterial pressure and increase in pulse pressure. Their conclusion was that licorice contains a substance with a DOCA-like action.

Confusion arose because a patient with Addison's disease did not react to the administration of licorice extract in the expected manner. For a time it seemed that licorice might be effective only in the presence of an intact adrenal gland, but Borst and others demonstrated that licorice had no action like ACTH; it produced no remission in patients with rheumatoid arthritis and it caused no decrease in eosinophil count. These conflicting observations made it necessary to repeat Borst's observations on the effect of licorice in another case of Addison's disease.

TABLE 1. *Chemical Determinations Made during Treatment of Addison's Disease with DOCA and Extract of Licorice.*

THERAPY	DAY	BLOOD UREA NITROGEN mg./100 cc.	SERUM SODIUM milliequiv./liter	SERUM POTASSIUM milliequiv./liter	SERUM CHLORIDE milliequiv./liter	SERUM BICARBONATE milliequiv./liter	TOTAL PROTEIN gm./100 cc.	HEMOGLOBIN gm./100 cc.	HEMATOCRIT %
Sodium chloride	8/15	30	132	6.75	100	17	7.7		
	8/28	70	132	7.55	104	18	8.3	15.2	45.0
DOCA	8/28	70	132	7.55	104	18	8.3	15.2	45.0
	9/5		136	5.35		23	6.3	11.4	33.5
	9/20	60	131	4.45	102	21			
DOCA and licorice..	9/20	60	131	4.45	102	21			
	9/30		134	4.25	101	25			
Licorice	9/30		134	4.25	101	25			
	10/9	25	142	4.5	111	28	6.68	13.7	40.5
Sodium chloride.....	10/9	25	142	4.5	111	28	6.68	13.7	40.5
	10/17	90	131	5.9	103	21	8.43	16.4	48.4
Licorice	10/17	90	131	5.9	103	21	8.43	16.4	48.4
	10/25	65	140	3.85	106	26	6.67	13.7	40.0
	11/18	23	139	4.55	107	24	7.45	14.0	42.0

CASE REPORT

A 34-year-old blind basket maker was admitted on August 15, 1950, to the Second Medical Service of the Wilhelmina-Gasthuis. For about a year he had noticed increasing fatigue and nausea with occasional vomiting after meals. Since June these complaints had increased so that he had stopped working. At about the same time he had feelings of faintness, "as if the blood ran out of his body and into the legs." He had also noticed an increasing appetite for salty dishes. He could no longer tolerate alcoholic beverages and his taste for cigarettes had gone. He was, however, remarkably free from migraine, from which he had suffered for most of his life.

In 1938 the patient had a glandular suppuration of the left side of the neck, which had healed after a course of x-ray irradiations. In February, 1949, a calcified tuberculous lesion had been detected in the upper part of the right lung in the course of a mass screening examination. Since then he had been under regular supervision, but the lesion was considered inactive. Several sputum examinations were negative for tubercle bacilli.

In 1942 the patient lost one eye as a result of a war wound; two months later the other eye was enucleated for sympathetic ophthalmia. Since then he has worn ocular prostheses and has had to change his profession to his present work of basket making.

On physical examination he seemed moderately well nourished (his weight was 53 kg.; height, 1.68 m.). The skin was slightly pigmented, but the areolae mammae were deep brown. The skin over the scrotum, penis and groins was dark brown; the oral mucous membrane showed patches of pigmentation. The venous pressure was normal, the heart was small; there was impairment of percussion over the right upper lobe. The abdominal organs appeared normal. The blood pressure was 110/95 on admission.

X-ray examination revealed fibrous induration of both apices, with multiple calcified lesions in the right upper lobe. The heart was small (Fig. 1*A*). There were no calcifications in the adrenal region.

On the following days, while the patient was being given 15 gm. of sodium chloride per day, the blood pressure varied between 115 and 95 systolic and 85 and 60 diastolic. The pulse ranged between 80 and 128. The electrocardiogram was normal; the urine contained no abnormal constituents; the sedimentation rate was 11 mm. in the first hour. Examination of the blood revealed a hemoglobin of 15.2 gm. and a red-cell count of 4,520,000. The white-cell count was 5600, with 3 per cent eosinophils, 56 per cent polymorphonuclear leukocytes, 38 per cent lymphocytes and 3 per cent monocytes. The hematocrit was 45 per cent. The total serum protein was 7.68 gm. and consisted of: albumin, 4.05 gm., euglobulin, 2.68 gm. and pseudoglobulin 0.95 gm.; the fibrinogen was 0.32 gm. The basal metabolic rate was +17 per cent. An oral blood-sugar test showed normal glucose tolerance, but blood-sugar samples taken at various times in the course of a regular day were never higher than 117 mg. The blood urea nitrogen was 50 mg. The urea clearance (van Slyke method) was 32 and 37 cc. per minute. An intravenous insulin-tolerance test was considered too hazardous. The water-excretion test of Robinson, Power and Kepler[6] showed a definite disturbance of water excretion. The night urine sample was 370 cc.; the largest day sample after a water load of 1.06 liters was only 250 cc. A Thorn test,[7] after injection of 25 mg. of ACTH, showed no drop in eosinophils, a maximum drop in the lympho-

TABLE 2. *Transverse Diameter of the Heart in Case of Addison's Disease during Treatment with DOCA and Extract of Licorice.*

DATE	THERAPY	DIAMETER OF HEART cm.	DIAMETER OF THORAX cm.	QUOTIENT
August 17	NaCl	9.7	28.5	0.34
September 11	DOCA 5 mg.	12.7	29.0	0.44
September 30	DOCA 1 mg. and licorice 15 gm.	11.5	28.8	0.40
October 10	Licorice 15 gm.	11.9	28.6	0.42
October 16	NaCl	10.7	28.4	0.37
October 23	Licorice 30 gm.	13.3	29.1	0.46

cytes of 25 per cent and a maximum rise in the uric acid-creatinine ratio of 40 per cent. The total excretion of 17-ketosteroids, determined in duplicate, was 3.6 and 2.3 mg. per twenty-four hours. Fractionation after the method of Dingemanse and Huis in't Veld[6] revealed that all fractions were low; dehydro-isoandrosteron was completely absent. The mineral composition of the serum revealed normal sodium and chloride contents. The potassium was increased (6.75 milliequiv. per liter) and the serum bicarbonate was diminished (38 vol. per 100 cc.).

A diagnosis of Addison's disease due to tuberculosis of the adrenal glands was made.

In the course of the observation the patient's condition deteriorated. In spite of the administration of almost 300 milliequiv. of sodium chloride a day, he felt weak, the body weight dropped to 52.5 kg., the blood pressure fell to 95/65; the blood urea nitrogen increased to 70 mg. per 100 cc. and the serum potassium level rose to 7.55 milliequiv. Hemo-

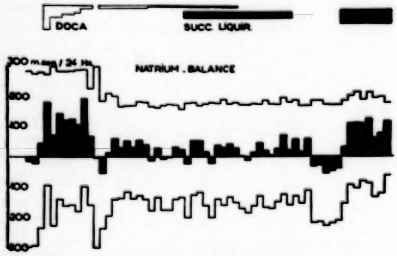

FIGURE 2. *Sodium Balance per Day.*
Sodium intake is represented above the zero line, urinary output below the line. The difference is represented in black either above (positive balance) or below the line (negative balance).

concentration became evident from a rise of total protein to 8.3 gm. per 100 cc. (Table 1). On August 28 the patient was given 20 mg. of DOCA intramuscularly, followed by 10 mg. daily for the next two days. In the following days the amount was gradually reduced. There was an immediate improvement in the condition: The pulse dropped to 80; the blood pressure, although continuing to fluctuate, rose to 120/85, and the body weight increased to almost 55 kg. In the blood there was a prompt response of the serum potassium, bicarbonate, protein, hemoglobin and hematocrit. The sodium balance, which had been negative, became positive, and the potassium balance, which had been positive, now showed an outpouring of potassium in the urine. After eight days of DOCA administration the patient showed signs of overdosage. The weakness had gone, but he now complained of a feeling of tightness over the chest, with shortness of breath, and he had several attacks of migraine. The neck veins were swollen to a level of 4 cm. above the angulus Ludovici; the heart was enlarged, on both physical and roentgenologic examination (Fig. 1*B*), and there was a systolic murmur at the apex.

Administration of desoxycorticosterone acetate was stopped for one day, which produced a prompt reversal of the sodium balance; the sodium chloride administration was reduced to 10 gm. per day and the patient was put on a regular dosage of 3 mg. of DOCA per day. On this dosage the patient felt well, but the sodium balance was still positive; after eight more days the DOCA intake was reduced to 1 mg. per day.

On this dosage the patient showed approximate sodium and potassium balance. After six days a 25 per cent solution of extract of licorice in water was added, in an amount of 15 gm. per day. The patient developed some diarrhea after the first few days, but apart from this no change was noted in his general condition. However, the body weight, which had remained stationary, rose sharply from 54 to almost 56 kg. during the nine days of combined administration of the two drugs. The sodium balance, which had been slightly positive when the patient was maintained on 1 mg. of DOCA, became more markedly positive on the combined intake. The potassium balance appeared to be positive, but this may

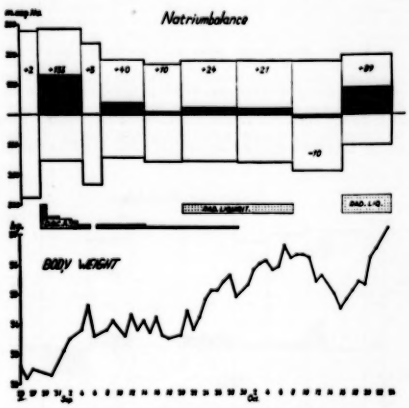

FIGURE 3. *Sodium Balance per Period.*
The figures indicate the average sodium balance per day during each period.

actually have been due to an increased loss of potassium in the stools, which were not examined at the time.

The favorable condition of the patient at the end of this period, both clinically and on laboratory examination (Table 1), and the apparent positive sodium balance encouraged us to withdraw the desoxycorticosterone at this stage. For the next nine days the patient was given 15 gm. of licorice extract only. The first day there was a small rebound in the

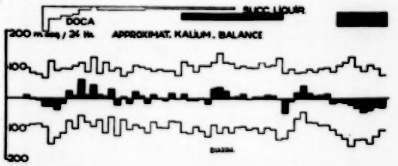

FIGURE 4. *Approximate Potassium Balance per Day.*
The balance has only approximate value because potassium intake was not determined by analysis but was calculated from the food intake, and because potassium losses in the stools were not determined but were assumed to be 10 milliequiv. per twenty-four hours. This was certainly too low during the time when the patient had diarrhea.

sodium excretion, with a corresponding drop of about 0.5 kg. in body weight, but on the following days the sodium balance was positive (with an average retention of 21 milliequiv. per day) and the body weight rose from 55 to 56.5 kg. The diarrhea had disappeared by this time, and the potassium balance was in equilibrium. The patient's condition remained excellent. Blood pressure and pulse rate were now normal. The heart did not decrease in size (Fig. 1*C*).

At this stage licorice extract was withdrawn. It was noted with interest that the sodium and potassium balances did not react to the withdrawal of the drug as promptly as they had done when DOCA was stopped. The potassium balance remained negative for two days before it began to show potassium retention; the sodium balance remained positive for three days before it became definitely negative. The patient remained without therapy for eight days. During this time the sodium balance became increasingly negative, with an average loss of 10 milliequiv. per day; however, if calculated over the last five (stable) days of this period, the average sodium loss was 41 milliequiv. per day. The body weight, which had remained stationary for two days after withdrawal of licorice, dropped in the next five days from 56.2 to 54.6 kg. Potassium was retained at an average of 12 milliequiv. per day. In the blood the urea nitrogen, which had become normal, rose to 90 mg.; the serum potassium remained normal for the first days, but on the last day of this period it rose to

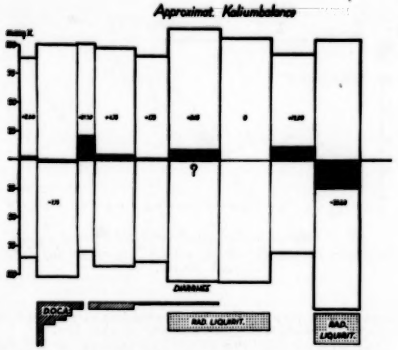

FIGURE 5. *Approximate Potassium Balance per Period. The figures indicate the average potassium balance per day during each period.*

5.9 milliequiv., with a corresponding drop in bicarbonate and rise in total protein, hemoglobin and hematocrit. The heart diminished in size (Fig. 1*D*). The patient complained again of feeling weak and, curiously enough, expressed a renewed desire for the licorice mixture.

During the next eight days the patient was put again on licorice, this time on a double dose of 30 gm. per day. The sodium balance reacted after one day and changed into a marked retention that almost equaled that of the period of DOCA administration. The average sodium retention during this period was 89 milliequiv. per day. The body weight increased in eight days from 54.6 to 57.2 kg. The potassium balance became increasingly negative (average loss, 25 milliequiv. per day). The patient experienced relief after one day. After one week the serum sodium had risen to the normal level of 140 milliequiv.; the licorice had produced a hypokaliemia of 3.85 milliequiv. and the hemoconcentration had disappeared. The heart had increased in size almost to the same dimension as after the overdosage of desoxycorticosterone acetate (Fig. 1*E*; Table 2). The whole course of the sodium and (approximate) potassium balance is represented in Fig. 2 to 5.

The chloride balance (not shown here) generally followed the sodium balance.

At this stage the dose of licorice extract was decreased to 20 gm. per day in an attempt to find a suitable maintenance dose. At the time of writing (November 28, 1950), the patient is in excellent condition after having been maintained on licorice extract only, with an intake of 10 gm. of sodium chloride per day, continuously since October 17. His general condition is excellent; the blood pressure is now regularly in the neighborhood of 120/80; there are no symptoms or signs of either over- or underdosage; the blood urea nitrogen is normal (23 mg.) and so are the mineral and protein constituents of the serum. The carbohydrate metabolism did not react — at least, there has been no rise in blood sugar to date.

DISCUSSION

The present observation confirms the conclusion of Borst and Molhuysen and their co-workers that licorice extract contains a substance with desoxycorticosterone-like action. The only difference that they and we have observed is that licorice seems to act more slowly than DOCA and that the rebound on withdrawal is less prompt. The fact that this substance is active when taken by mouth is also worth noting; it may very well give licorice, or its active principle, a prominent position in the future treatment of Addison's disease. Dr. Borst has seen our patient and is convinced of the positive result. Why his patient did not react to licorice, whereas our patient did, remains an open question.

The discovery of the activity of licorice in the treatment of Addison's disease fills the physician with feelings of both amusement and modesty. Pernicious anemia (also described by Addison) was for many years an incurable disease, while liver was available at every butcher shop. It now appears that one could have bought in every Dutch candy shop the substance that may save the life of a patient with Addison's disease. It makes one wonder how many more medical treasures of this kind are on exhibition in the windows of our grocery stores. Medical research is surely wonderful, but it sometimes achieves simple aims in complicated ways.

SUMMARY

A case of Addison's disease has been described that after preliminary treatment with desoxycorticosterone acetate showed maintenance of mineral equilibrium on the administration of 15 gm. of extract of licorice per day. Withdrawal of the extract was followed by reappearance of the clinical, biochemical and hemodynamic disturbances. A second course of 30 gm. of licorice daily again produced sodium retention, potassium loss, reversal of the abnormal hemoconcentration and a clinical remission. This observation confirms the finding of Borst and his associates that extract of licorice contains a substance with DOCA-like action that is active on oral administration.*

ADDENDUM

Since this article was submitted for publication we have treated a second patient. Through the kind co-operation of Dr. Borst and Dr. de Jong a crude preparation of one of the main ingredients of licorice was employed. The daily oral administration of 3.3 gm. of ammonium glycyrrhizinate kept this patient, previously maintained on 2.5 mg. of DOCA

*The authors are indebted to Miss C. P. Raderama, dietitian to the Second Medical Service, for her highly skilled assistance.

daily, in sodium, potassium and chloride equilibrium. Glycyrrhizonic acid is a component of glucuronic acid and glycyrrhetinic acid. The latter is a polyterpene with a structural formula exhibiting a striking resemblance to the cyclopentanophenanthrene steroids to which desoxycorticosterone belongs.

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EVENTRATION OF THE DIAPHRAGM REPAIRED WITH TANTALUM MESH*

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IT HAS long been considered that eventration of the diaphragm is a condition not amenable to surgical therapy. Furthermore, the opinion has been held that while distressful symptoms may be associated with eventration, serious complications do not occur. Graham[1] quotes Clopton to the effect that "the prognosis in the cases of eventration is good and death has never been observed as a direct consequence of the condition." He notes that complications, "other than those which arise from the involvement of the organs that enter into the abnormal displacement, are rarely more serious than are seen with normally placed viscera."

Recently, two cases of eventration in infancy, treated surgically, have been reported: the first by Bisgard,[2] treated by reefing through a thoracic approach and the second by State,[3] in which an abdominal approach was used. In both these cases respiratory embarrassment was the indication for operation. In both cases the diaphragm was muscular and of considerable substance and retained sutures well. Bisgard remarks that "much less might be expected of cases in which the diaphragm is a thin, fibrous membrane, which apparently is the more common condition." State concludes: "It would be difficult to do a surgical repair on such thinned, atrophic diaphragms."

Reed and Borden,[4] in 1934 reported two cases and reviewed 183 cases found in the literature. There were 165 cases involving the left leaf and 18 involving the right — a relative incidence of 9 to 1. They listed as symptoms of which patients with eventration complain: abdominal pains, vomiting, dyspepsia, constipation, dysphagia, heartburn, palpitation, tachycardia, dyspnea and cyanosis. These authors concluded that medical management is the treatment of choice and a "review of surgical management leaves one with the impression that such treatment offers little hope of cure."[4]

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Case Report

A 65-year-old businessman was admitted to the Bridgeport Hospital in August, 1948, in shock after vomiting considerable old and fresh blood. He was 6 ft., 2 in. tall and weighed 220 lb. on entry. He had lost about 20 lb. in the past six months. He was transfused and placed in an oxygen tent and remained in a precarious condition for a week. On admission the red-cell count was 800,000, with a hemoglobin of 20 per cent. He was given 9 pints of blood over the course of two weeks and was kept in an oxygen tent. A gastrointestinal series showed that the right diaphragm was elevated to the third interspace on the right (Fig. 1 and 2) and the duodenum was pulled over so that it was on a level with the esophagus, and in the right chest. The x-ray films were interpreted as showing an "anomalous position of the

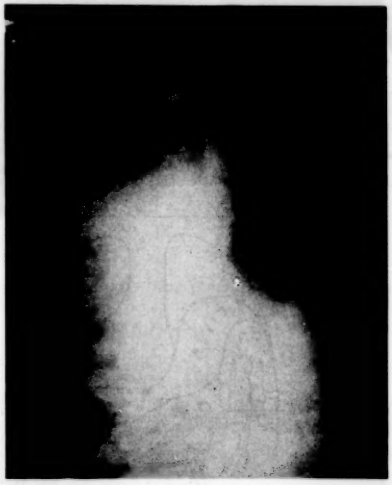

FIGURE 1. *X-ray Film (August, 1948) showing Elevated Right Diaphragm.*

stomach and duodenum, the appearance of which suggests that the stomach is under traction, and there is evidence of partial obstruction about the region of the duodenum, most probably on the basis of a mechanical obstruction, related to the anomalies discussed above. The possibility of a duodenal ulcer is not excluded." At the end of two weeks he was discharged.

He had considerable gas and discomfort in the right upper quadrant during his stay at home. He was placed on an ulcer regime and followed it conscientiously. However, he failed to gain in strength and continued to have tarry stools.

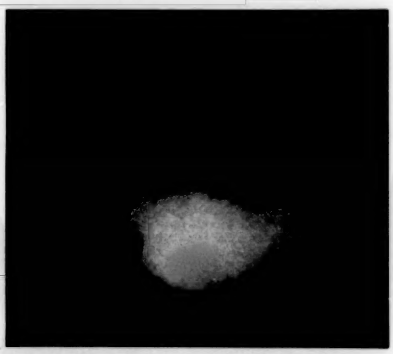

FIGURE 2. *Position of Stomach with Duodenum on a Level with the Esophageal Hiatus.*

He was readmitted for study on March 7, 1949, when I saw him for the first time. His red-cell count was 2,800,000, with a hemoglobin of 40 per cent and a nonprotein nitrogen of 34 gm. per 100 cc. An electrocardiogram showed right-axis shift. The blood pressure was 160/84.

It was decided that surgical interference was necessary. In view of the fact that considerable distortion of the stomach

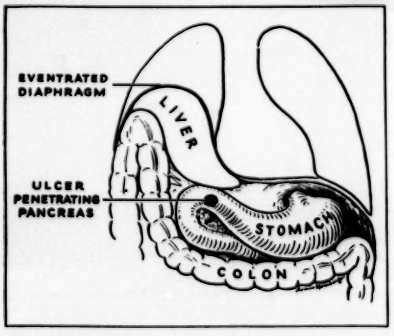

FIGURE 3. *Diagram of Situation Found at First Operation.*

existed, it was thought that an attempt should be made to restore the abdominal structures to their normal position. The patient was given 4 pints of blood over a period of ten days, which raised his red-cell count to 4,100,000 and his hemoglobin to 63 per cent. He was given 500 cc. of blood on March 15 and the same amount on the following day.

At operation on March 16 the 9th rib was removed and the chest entered. A thin eventrated diaphragm was found and opened. A large indurated duodenal ulcer was noted and the structures as shown in Figure 3 were found in the chest. It was considered unwise to resect the ulcer — indeed, it would have been technically impossible. The diaphragm was then closed and plicated twice with rows of interrupted sutures. A sheet of tantalum mesh was then placed and sutured over the dome of the diaphragm with tantalum wire sutures. It was noted that the phrenic nerve was narrow and pale. The diaphragm moved slightly in a paradoxical manner. The lung was fully inflated with some difficulty and the lower margins of the lower lobe were rounded as if restrained from expansion by fibrosis within it. The chest was not drained.

The patient had considerable drainage from the Levine tube for the first three days after the operation. His abdomen was distended but soft. Respirations were shallow and fine rales were heard over the left lower lobe. An x-ray film showed 25 per cent pneumothorax on the right and increased den-

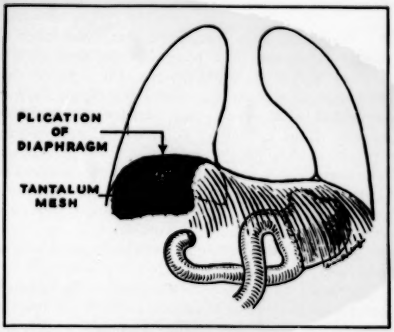

FIGURE 4. *Diagram of Diaphragmatic Repair and Subsequent Gastric Resection.*

sity in the left lower lung field. The patient was cyanotic in the tent. The right chest was aspirated; 1075 cc. of air and a small amount of serosanguineous fluid was obtained. The trachea was aspirated and some thick, tenacious secretions removed. CO_2 inhalations were given at intervals, and the patient's color improved considerably. These symptoms cleared in the course of a week and he was allowed out of bed on the 6th day. His vital signs were normal, but he had considerable gas. He was given a high-protein liquid mixture with gruel and soft-boiled eggs. On the 10th postoperative day the patient had several tarry stools. On the 17th postoperative day he vomited large quantities of coffee-grounds material. On the 18th day he vomited a pint of dark blood and went into shock, his blood pressure dropping to 72/38. He was transfused and the blood pressure returned to a satisfactory level. The following evening he vomited more blood and his blood pressure dropped to 60/0. His red-cell count was 2,950,000, with a hemoglobin of 45 per cent. He was taken to the operating room.

Under intratracheal gas-oxygen-ether anesthesia a 6-inch left-upper-rectus incision was made and the peritoneum opened. The stomach was found to be enormously distended; suction on the inlying Levine tube was of no avail. A trocar was therefore inserted into the stomach and large quantities of blood, clots and air were removed. A gastric resection was done, dividing the duodenum distally to the ulcer, which was situated at the pylorus. In freeing the pyloric area from the head of the pancreas it was found that an ulcer 2 by 3 cm. had penetrated the head of the pancreas to the depth of 1 cm. In the floor of the ulcer a clot was brushed off an artery, presumably the gastroduodenal artery, with a resultant vigorous

flow of blood. The vessel was grasped with a Kocher clamp and sutured. No attempt was made to excise the ulcer bed (which was in fact pancreatic tissue), the stomach being trimmed around it. A short-loop anterior Polya anastomosis was done after resecting approximately three fourths of the stomach. A drain was inserted as far as the ulcer defect in the head of the pancreas. The patient received 2500 cc. of blood during operation, under pressure until his blood pressure was stabilized and the source of bleeding was under control. He left the operating-room in good condition. The diaphragmatic repair was noted to be intact and the liver in its normal position at the costal margin.

He had some abdominal distention, rales at the left base and liquid stools of old blood for the first two postoperative days. On April 6 the red-cell count was 3,270,000, the non-protein nitrogen 119 gm. and the CO_2 44. Fluids brought the nonprotein nitrogen down to 31 gm. in four days. He received 1000 cc. of blood on April 6. He gradually improved in strength, his appetite became ravenous and he was discharged twenty-four days after his second operation. Some drainage persisted from the wound for about two weeks postoperatively. In all, the patient received twenty transfusions of 500 cc. of blood each during this admission. X-ray films of the chest showed the diaphragmatic repair to be intact and the lung to be expanded, with minimal fluid.

He returned to work in a month and since that time has been in excellent health, working at an exacting job requiring a moderate amount of physical labor. His appetite has been good, and his weight has gone gradually from 188 to 223 lb. (on June 2, 1950). X-ray films taken on June 2, 1950 show that the diaphragm is retaining its position.

Comment

The reactions of the tissues to tantalum mesh have been described by Koontz[5, 6] in a series of careful studies. He has shown that the mesh becomes thoroughly infiltrated with fibrous tissue. It was for this reason that tantalum mesh was used in the case presented, with the purpose of adding the temporary strong support of the mesh itself, and the permanent strength of firm scar-tissue to the inadequate thin membrane of an eventrated diaphragm. Koontz has also shown that in dogs tantalum mesh may be placed next to bowel in abdominal defects, with merely a few light adhesions as a result. From the experience with the case here reported, it may be concluded that tantalum mesh can be placed next to the lung without harmful effects and with no more effusion than one would expect to occur after an exploratory thoracotomy.

Discussion

I have seen 4 cases of eventration in the past three years; 3 of the 4 presented complications. Two patients had massive gastric hemorrhage; the other had a perforated ulcer, followed by a left subphrenic abscess. This is undoubtedly unusual, yet discussion of the subject with other surgeons has brought to light cases of eventration having complications of various types. It is possible that conclusions regarding the benignity of the condition have been based for the most part on series of cases uncovered by routine x-ray examinations and that complicated cases have not found their way into the literature.

Summary

A case of eventration of the right leaf of the diaphragm associated with massive hemorrhage from a duodenal ulcer is presented. The patient was explored thoracically; the diaphragm was pleated and reinforced with tantalum mesh. Subsequent bleeding necessitated an emergency gastric resection.

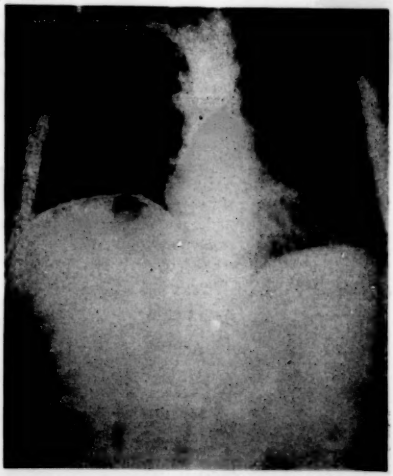

Figure 5. *X-ray Film (June 8, 1950) Showing Tantalum Mesh and Repair Intact.*

X-ray films taken fifteen months after operation show the repair to be intact and the diaphragm remaining in its new position.

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FIFTY YEARS OF MEDICAL PROGRESS

MEDICINE AS A SCIENCE: PATHOLOGY*

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BOSTON

IN REVIEWING the progress of pathology during the first half of this century, it seems more interesting to consider the changes in viewpoint and emphasis that have taken place in this branch of medical science than to list a specific group of outstanding publications. Since the field of pathology is that which deals with the responses of living tissues to unfavorable influences, it serves as a focal point, contributing to and receiving contributions from nearly every other field of medicine, as well as from physics, chemistry and biology. Along with remarkable changes in its related sciences, pathology has undergone so great a metamorphosis in the last fifty years that it has interests that differ greatly from those of pathology in 1900. Nevertheless, there remain at its core the diagnostic obligations that have characterized it since the time of Virchow and to which the somewhat patronizing name of "routine hospital pathology" is often given.

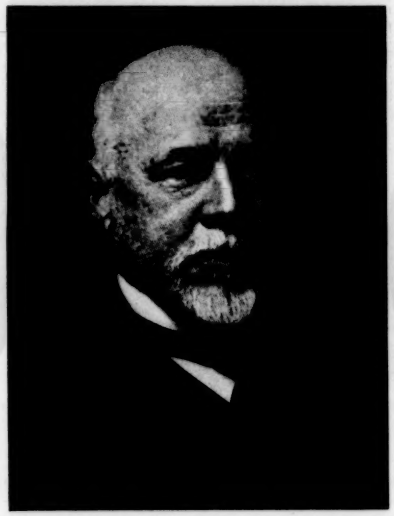

FIGURE 1. *William H. Welch, M.D. (Reproduced from Burket, W. C.* Bibliography of William Henry Welch. *Frontispiece. Baltimore: Johns Hopkins Press, 1917, by Permission of the Publisher).*

At the beginning of the century, pathology in the United States was in the process of emergence as a separate field and was still in the shadow of the great nineteenth-century Germans who created the science, notably Virchow, Cohnheim and Rokitansky. Since a detailed knowledge of diseased organs was then regarded as a necessary part of the clinician's training, a large number of young men went each year to study pathology in the great medical centers of Europe, especially Vienna and Berlin. In the early years of the century, however, there were at least three notable departments of pathology in the United States — one in Baltimore, another in Boston and a third in New York. In Baltimore, Dr. William H. Welch, a leader in morphologic and experimental work, was training a distinguished group of pupils who were to extend the field of pathology throughout the country. One of these pupils, Dr. William T. Councilman, came to Boston in 1892 as Shattuck Professor of Pathological Anatomy at Harvard Medical School. Somewhat later Dr. Frank B. Mallory, after a period of training in

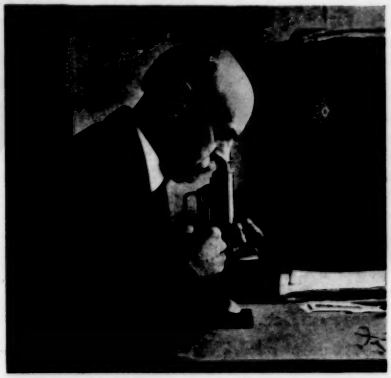

FIGURE 2. *Frank B. Mallory, M.D. (Reproduced from Leary, T.* Frank Burr Mallory and Pathological Department of Boston City Hospital. *Am. J. Path. 9:659, 1933, by Permission of the Publisher).*

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Germany, established himself in Boston, devoting his attention, like Dr. Welch, to the training of pathologists and to the detailed study of diseased human tissue as revealed by means of new technical methods devised by himself. In New York, Delafield and Prudden were about to publish, from their excellent laboratory, one of the earliest influential American textbooks of pathology. All three centers had been established before 1900, but their recognition came at about that time. These and other American groups began to attract more and more men for training, a process greatly accelerated after World War I. With the advent of the Hitler regime, pathology in Germany suffered perhaps more than any other field in medicine at a time when American pathology was making rapid progress.

Because of the services that the pathologist can render to the clinician in the diagnosis of tissues at operation or post-mortem examination, the purely descriptive aspects of the science are usually better known to those outside the field than are the contributions that pathology has made to the understanding of disease mechanisms. A single examination of a diseased organ can yield a picture of only one stage of the process, whereas the study of a series of tissues in different stages can furnish information on the sequences of disease, especially at the cellular level. This method has proved of great value when applied to human tissue and supplements the contributions made by other technics in experimental study.

In the years 1900 to 1950, much emphasis has been laid on the physiologic aspects of pathological studies. The leader in the publication of the philosophy of dynamic pathology was Alonzo Taylor, who was followed by Richard Pearce and Howard Karsner. This interpretation, whether formally stated or not, has been a mainstay of pathological investigation from its beginning but has been extensively implemented by the increased complexity of technics and by the variety of problems studied in the past fifty years.

Of the numerous ways in which pathological studies have contributed to the understanding of disease, an important one is found in the suggestions for the direction of experimental work that have derived from studies of human material. An illustration is the impetus to clinical investigation that came from a single case report by Opie. This report described hyalinization of the islands of Langerhans in a patient dying of diabetes mellitus and suggested an etiologic relation. Although it soon became apparent that the lesion is not constantly present in diabetic patients, the paper focused attention on the role of the islands of Langerhans in diabetes and pointed the way to further investigations that have greatly increased the available knowledge of the physiology and therapy of the disease. MacCallum's studies on the parathyroid glands have much the same relation to subsequent studies of the normal and abnormal functions of those organs. These are only two examples of a large group.

The contributions that pathologists have made to the diagnosis and prognosis of disease have usually resulted from the study of series of carefully selected cases. An obvious example is that of cancer behavior, with which the names of F. B. Mallory and James Ewing are especially associated in the period covered by this report. The histologic grading of tumors also falls in this group. On the experimental side, the transplantation studies of Green have greatly influenced our thinking on the autonomy of malignant tumors. Another important publication of results obtained from the careful study of a series of cases is Percival Bailey and Harvey Cushing's "Tumors of the Glioma Group," which furnished systematic classification of these tumors and put in perspective a chaotic mass of uncorrelated publications.

The practice of pathology has been influenced and expedited by the development of various registries of pathological material, now collected in one group at the Armed Forces Institute of Pathology in Washington. These registries are the outgrowth of the Registry of Bone Sarcoma, founded in 1919 by E. A. Codman. Experience gained in this way has shown that judgment in diagnosis and prognosis must rest not alone on histologic criteria but also upon known end results in large series of cases. A given microscopical picture can then be related to known behavior of the lesion. The Registry of Bone Sarcoma, for instance, produced conclusive evidence that the giant-cell tumor of bone is a benign lesion, in spite of the fact that it possesses many of the criteria of malignancy as seen in a microscopical section. The amount of experience that the pathologist can obtain, even in a large hospital, is very small in comparison with the accumulations already available in present-day registries. On the other hand, this development has tended to make the dividing line between practice and research in pathology even sharper than before — a condition that has considerable disadvantages.

In 1900, bacteriology was a division of pathology in most medical schools and hospitals. With the rapid increase in the importance of immunologic research and with developments in technics for studying micro-organisms, the two fields have become more widely separated, a process further increased by the advent of chemotherapeutic drugs and antibiotics. In spite of this, contributions of major importance have been made to the field of infectious diseases by pathologists with training and interest in bacteriology. Wolbach described the etiologic agent and the specific lesion of Rocky Mountain spotted fever. He later combined morphologic and experimental research to establish which of several suggested agents might be the cause of typhus fever. These two investigations

formed the foundation upon which present knowledge of rickettsial diseases rests. So, too, much of the initial work on infections due to filterable viruses was the product of pathologists with additional experience in bacteriology. The work of Flexner on poliomyelitis might be cited as an example. Of special importance is the first demonstration of a filterable virus as a cause of tumors in the experimental animal — the Rous chicken sarcoma. This work is important not only because of its relation to the etiology of human cancer (in which viruses as such do not have much part, so far as is yet known) but also because of its information on the general behavior of malignant tumors, which has resulted in further studies of this virus and of the Shope papilloma virus.

Another important contribution combining pathology and bacteriology was that of Goodpasture in developing and applying the technic of inoculation of the chorioallantois of the hen's egg. It has been the stimulus to many fruitful investigations of the pathology of bacterial infections, of virus diseases and of the participation of specific cells in the immunologic processes.

The recognition of the untoward internal responses in anaphylaxis and in hypersensitivity in general gave an impetus to new experimental work throughout the medical world. To the pathologist it brought a new attitude toward interpretation of histologic changes. An important recent contribution in this field is Rich's experimental and morphologic evidence that allergic arteritis is the pathology of serum sickness and that it is probably identical with periarteritis nodosa. These findings raise questions concerning the histologic criteria of infectious processes, for certain stages of periarteritis nodosa are very similar to equivalent stages of rickettsial diseases. In the lesions of rickettsial diseases the organisms can be demonstrated, whereas in those of periarteritis nodosa we are dealing with an abnormal immunologic state without direct participation of micro-organisms.

From this discussion of combined bacteriologic and pathological research, one is forced to the conclusion that important contributions from pathologists have resulted when they combined the technics of related sciences with the methods and ideas of their own field. This is equally true for the pathologists who have applied the newer chemical technics to the problems involved in the responses of cells to unfavorable conditions. The use of tissue culture at once suggests itself, but the most important results of this technic have been in fields other than pathology. On the other hand, depriving animals of compounds of known chemical composition has led to precise information on the cells requiring them and on cellular behavior resulting from this deficiency. This is another way of saying that knowledge of the pathology of vitamin deficiencies has advanced understanding of chemical participation in specific cellular activities. In this field the work of Wolbach is pre-eminent. He not only described the lesions of deficiency in vitamins A, C and D but illustrated how these deficiencies might be used as technics of biologic investigation. Pappenheimer did much the same for Vitamin E. The deficiency lesions of the B group of vitamins are less clearly understood. It is of the greatest interest to pathologists, however, that Peters was able to prove that the participation of Vitamin B_1 in cellular metabolism takes place in pyruvate metabolism. The changes visible by microscope are variable and secondary. Vitamin B_1 deficiency, then, is an example of a fundamentally biochemical lesion.

The effects of withholding essential amino-acids have also been extensively explored, notably by Rose. Precise characterizations of these deficiencies at the cellular level are for the most part lacking; this seems a promising field for further study.

Alonzo Taylor, in implementing his ideas of dynamic pathology, carried on pioneer studies of cellular enzymes, but this field has not yet produced so many significant results as would seem possible with further exploration. The development of microchemical technics by Lindestrøm-Lang and others offers a means of exploring many chemical changes and enzyme reactions at the cellular level. These technics are now being used by numerous investigators and should add significantly to the understanding of diseased tissues within the next few years. There is also an increasing number of so-called histochemical technics; these are essentially qualitative but have the advantage of identifying the exact cellular location of compounds. These methods have been developed by Feulgen, Gömöri, Wislocki, Dempsey and many other workers. Their usefulness in the study of pathologic processes is only beginning to be explored and, in fact, cannot be fully tried until more information on normal tissues is obtained.

Another interesting development of the past half-century, combining chemistry and pathology, is the discovery by many workers, and in many places, of chemicals the application of which regularly produces tumors in experimental animals. This followed the observation of Yamagiwa and Ichikawa in 1914 that the repeated application of coal tar produced tumors, a few of which metastasized, in experimental animals. A search for the active compound in coal tar responsible for the effect brought to light several substances that were far more effective than crude coal tar — and of which the chemical structure was known. Among them were dibenzanthracene, methylcholanthrene and benzpyrene. Since some of these were related in structure to the sex hormones, it was thought possible that considerable light might be thrown on the pathogenesis of human cancer. Although these expectations have not as yet been definitely fulfilled, work with these and other carcinogenic compounds has contributed to the recognition of tissue

changes antecedent to the formation of at least some types of cancer.

It would not be fitting to leave the subject of chemistry in pathology without reference to Wells' "Chemical Pathology." In its successive editions it brought together much scattered information on the chemistry of diseased tissues and kept pathologists aware of the importance of chemical work in their specialty. It is true that most of the material in Wells' book dealt with mass analyses of tissue, the only analytical methods available until recently. One of the reasons that the newer procedures of microanalysis are so important to pathologists is that they free the investigator from dependence on determinations using organs made up of many diverse cells and tissues.

The developments of physics in the last half-century have left a definite imprint on pathology. From the time of the discovery of roentgen rays and radium, the importance of the cellular changes caused by these physical agents has been a concern of the pathologist, especially in following and predicting their influence on tumors. This concern has been greatly accelerated by the necessity of studying the effects of atomic warfare. Many groups have participated in this work, especially that of Warren and his co-workers. The changes due to atomic bombing are essentially mass phenomena, but the availability of radioactive isotopes now permits specific planned experiments. These, like the newer chemical methods, should permit more precise studies of cellular behavior in abnormal states.

The invention and development of the electron microscope made available to the pathologist another potentially helpful technic. Valuable as such an instrument might at first appear for tremendous magnification of structures, it has as yet a restricted usefulness in the direct study of diseased tissues. One of its most serious limitations is the fact that all material to be examined must be in the dry state, thus potentially introducing at least as many artifacts as are present in the usual histologic preparation. Schmitt's demonstration of the fine structure of collagen is the result perhaps most interesting to pathologists so far, although direct application to diseases involving collagen has not yet been made.

From the foregoing discussion, it is clear that a great expansion of pathological research resulted when accessory disciplines were brought to bear on the problems to be studied. In the 1930's the need for dual training had become clear to men who planned to devote themselves to the field. An increasing number incorporated from one to three years' work in some other field in their preparation for pathology. Without personal training and experience in the supplementary technics, use of them can only be made at the amateur level.

This trend has not continued, productive as it has proved to be. One important impediment to it was the situation arising from the needs of the armed forces in World War II. The number of pathologists is never large in comparison with that of internists and surgeons. Very few hospitals and medical schools have pathological departments with more than the minimum personnel required for operation. During the war, each military hospital needed one or more pathologists, and others were necessary for such agencies as the Office of Scientific Research and Development. Civilian hospitals, therefore, had to operate with insufficient pathological staffs, and few men could be spared for prolonged training. In the armed forces, inadequately trained pathologists had to be employed under conditions in which supervision was impossible. Since few new pathologists had been trained during the war, these men were readily able to find opportunities on their return to civilian life without obtaining additional training. This was accelerated in those parts of the country where pathologists are paid on a fee basis and in consequence receive much higher incomes than those on salary. Although the effect of World War II was felt in the training of men in every branch of medicine, it has been especially serious in pathological investigation.

In 1936, the American Board of Pathology was organized, along lines similar to the boards of certification in other medical specialties. The group has been successful in establishing minimal criteria for training in pathology. Its requirements emphasize morphologic work, with or without experience in the procedures of clinical pathology. In securing the qualifications for Board certification, the man who expects to become a pathologist often finds that the time necessary for work in an accessory field has slipped away.

Within the fifty years covered by this report the position of pathology as a specialty has been reversed. In 1900 it was held in very high regard but had produced comparatively little research in the United States. Today, with a record of great accomplishment, it is much lower in medical esteem. Perhaps the greatest hazard in the field at present is the possibility that experimental pathology will be performed by those lacking detailed experience in human disease, while diagnostic pathology is carried out by others not alert to its possible contribution to further knowledge of the responses of living tissue to untoward influences.

The field of pathology, as defined in this report, is entitled to its own place among the biologic sciences. The types of phenomena that it treats are deserving of further investigation. If studied with the full armamentarium of approaches that are currently available or that may be developed, pathology can continue to make contributions to the understanding of living processes different from those produced in the fields of physiology, biochemistry or clinical investigation.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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CASE 37131

PRESENTATION OF CASE

A thirty-nine-year-old woman entered the hospital with the complaint of severe back pain.

Five years and three years prior to admission the patient had sustained apparently minor injuries in automobile accidents, with resulting pain and stiffness in the neck, which responded readily to diathermy. One year prior to admission she noted sharp pain under her shoulder blades, radiating into her neck, that was aggravated by motion; this disappeared after chiropractic massage. Six months before entry she began to feel unusual fatigue and had a recurrence of pain near the shoulder blades that again responded to chiropractic treatment. A month later she developed a constant ache in the right scapula; it was aggravated by motion and became sufficiently severe to interfere with sleep. It did not respond to osteopathic therapy but gradually spread to involve both sides of the back parallel to the scapular spines. Three months before admission she also developed extreme soreness over the sternum. A month later, sharp pain appeared over the left and right lower ribs in the anterior axillary line and was followed by a constant aching soreness. She had lost eleven pounds during her illness on a voluntary reducing diet, but had no other systemic symptoms of any description. One month before admission she entered another hospital, where physical examination revealed a well nourished, well developed woman in no apparent distress and with normal pulse, temperature and respirations. The blood pressure was 130 systolic, 70 diastolic. There was one palpable lymph node in the left posterior cervical triangle. The right upper lobe and isthmus of the thyroid gland were felt; no nodules were demonstrated. There were decreased breath sounds and moist rales at the right base. The heart was unremarkable. No abdominal organs or mass was felt. There was tenderness over the second and third thoracic vertebras. Neurologic examination was negative. The blood, urine and routine chemical determinations were unremarkable. No Bence–Jones protein was found. The blood and spinal fluid gave negative Wassermann reactions. A lumbar puncture yielded clear fluid under an initial pressure equivalent to 130 mm. of water, with normal dynamics. The cerebrospinal fluid contained no cells and had a total protein of 60 mg. per 100 cc. A retrograde pyelogram and a gall-bladder series were negative. X-ray films of the spine revealed a "pathologic fracture" of the third thoracic vertebra. The cervical lymph node was biopsied and was reported to be chronic inflammation. The back pain responded well to 1460 r of x-ray therapy administered in seven doses. The patient was then referred to this hospital for further study. Two days before admission she developed pain in the left sacroiliac region, radiating down the leg, that was similar to but more severe than the usual premenstrual pain. The last menstrual period, which started a week before admission, was more profuse than usual, but she had noted no intermenstrual bleeding or hot flashes.

Physical examination on admission revealed findings similar to those made at the other hospital, except that the lungs were now clear and a tender liver edge was felt 3 fingerbreadths below the costal margin. The upper thoracic spine, sternum and left sacroiliac region were exquisitely tender. The spleen was not felt. The breasts were well developed and soft throughout. Pelvic examination revealed an irregular orange-sized mass occupying the region of the uterus and extending into the right vault and posterior cul-de-sac. The cervical os was surrounded by a 1.5-cm. area of red erosion. Neurologic examination was negative.

The urine had a specific gravity of 1.020, gave a negative test for albumin and contained 3 white cells per high-power field and no casts in the sediment. Examination of the blood disclosed a hemoglobin of 11.8 gm. and white-cell count of 5400, with 58 per cent neutrophils, 29 per cent lymphocytes, 11 per cent monocytes and 2 per cent eosinophils. The platelets appeared normal. The sedimentation rate was 16 mm. per hour. A blood Hinton test was negative. The nonprotein nitrogen was 17 mg., the total protein 6.59 gm., with an albumin-globulin ratio of 1.9, and the alkaline phosphatase 2.4 units per 100 cc. Smears of the urine and vaginal contents revealed no malignant cells. An intravenous pyelogram and barium-enema examination were negative. Films of the lung fields, lumbosacral spine and pelvis were unremarkable. However, part of the body of the third dorsal vertebra was seen to be collapsed, with anterior wedging and resulting kyphosis of the spine. A small paravertebral soft-tissue mass surrounded the partially col-

lapsed body, above and below which the disk spaces were well preserved. Agglutination tests for typhoid and undulant fever were negative.

An aspiration biopsy of the soft-tissue mass that had been seen on the x-ray film near the third dorsal vertebra was attempted under x-ray control, but with the needle in proper position on four successive trials nothing could be obtained except a free flow of arterial blood. On the fifth hospital day an operation was performed.

Differential Diagnosis

Dr. Joseph S. Barr*: I do not quite understand why the patient shifted from a chiropractor to an osteopath, when she had been relieved of pain by a chiropractor. Patients nearly always tell us that their pains were relieved by an osteopath or chiropractor — and then we find them in our offices.

From the history and physical findings, it seems quite obvious that the physicians in charge thought that this patient had a fracture due to a neoplasm — a pathologic fracture. They searched long and diligently for a primary focus, presumably did not find one, attempted an aspiration biopsy, obtained blood and then proceeded to a biopsy.

Aspiration biopsy of vertebral bodies is relatively safe and in some cases is a satisfactory way of making a diagnosis, but the anatomical location of the lesion is most important. From the ninth dorsal vertebra distally, the aspiration can be made with relative safety; from the ninth up to and including the first dorsal vertebra, it is a procedure that should be undertaken only with extreme caution, and perhaps should not be undertaken at all. There are large structures of great importance in that area. I think that it was fortunate that nothing occurred but a free flow of blood that stopped when the needle was removed. The lower cervical vertebras can also be safely needled.

We might see the x-ray films and then continue the discussion from that point. I think Dr. Wyman will say that the third dorsal vertebra is one of the most difficult to outline and visualize by x-ray examination. Satisfactory bone detail is often missing in routine films.

Dr. Stanley M. Wyman: I agree with Dr. Barr's statement. The vertebra in question seems to be considerably narrowed and wedged in relation to the vertebra above and below it, and the vertebral body appears less dense than usual. There is a suggestion of some soft-tissue fullness at the right of this vertebral body, as seen in the anteroposterior projection. A film of the barium-enema examination discloses no definite abnormalities. The lung fields likewise are not remarkable. The heart shadow is somewhat prominent in the region of the left ventricle. The lumbar spine, other than being held rather rigidly, shows no definite abnormality. Although the kidneys cannot be well outlined in the pyelogram because of material in the bowel (and the concentration of the dye that was excreted was rather poor), the left kidney does seem larger than the right. The calyceal system of the left kidney seems to lie unusually far from the upper pole of the left kidney, and I think the upper pole may be fuller than usual. These are not definite findings, but I think the patient might well have had a retrograde pyelogram.

Dr. Bernard Jacobson: The retrograde pyelogram was negative about a month prior to entry here. The films were excellent.

Dr. Barr: Is this soft-tissue paravertebral mass well localized to the vertebra?

Dr. Wyman: It is a very indefinite thing, Dr. Barr. I cannot outline its border at all well.

Dr. Barr: Dr. Wyman has shed a little additional light — or perhaps he has brought forth a "red herring." There is some evidence that the left kidney was not normal.

A thirty-nine-year-old woman had two minor injuries five and three years prior to admission. She had interscapular pain a year before admission that finally became constant, after which she developed pain over the sternum and about the ribs and then in the left sacroiliac region radiating down the leg. She had lost some weight, but it was "due to a diet." She had a lymph node in the cervical triangle, which was biopsied and showed chronic inflammation. She also had a mass in the uterus, but after investigation of the secretions from the vagina it apparently was dismissed by the examiners; I suppose it represented a fibroid. The cerebrospinal-fluid total protein was elevated mildly, perhaps due to local irritation of the dura, but she had no evidence of actual pressure on nerve roots or on the spinal cord. X-ray therapy given at an outside hospital was said to have produced some relief. The relief may have been due to two things: first, the anesthetic effect of x-rays, which makes almost any sort of painful lesion feel better temporarily, or secondly, a possibly radiosensitive type of malignant process.

I shall discuss some of the lesions that may cause collapse of vertebras. She had trauma some years previously, but the trauma was insufficient. It requires severe trauma to fracture the third thoracic vertebra, protected as it is by the thoracic cage. Moreover, in the case of trauma, there would have been sclerosis about the lesion; this was an osteoporotic type of lesion. Postmenopausal osteoporosis is perhaps the next most common cause of a collapse of the vertebra — but this patient had not reached the menopause. Tuberculosis — Pott's disease — is a very common cause, but usually the intervertebral space on either side is involved, and narrows early. As a rule, more than one vertebral body is involved, and there may be a paravertebral abscess dissecting downward over more than one space. Was a tuberculin test done?

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DR. JACOBSON: There was a positive tuberculin reaction: 1:100 (precipitated-protein derivative).

DR. BARR: If that had been negative I should have dismissed tuberculosis at once. However, I can only say that at some time in the past she had been sensitized to tuberculin. She had severe pain, marked localized tenderness and night pain. As a rule tuberculosis — although it causes pain, muscular spasm, limitation of motion and so forth — does not cause as severe pain or such severe local tenderness as this woman had. I think tuberculosis is unlikely. Other infectious processes — pyogenic infections and typhoid fever were considered, but no evidence for them was found.

I cannot readily think of any primary malignant tumors that produce a pattern such as this, and I should agree with the physicians who saw this patient that it was probably a metastatic process. It is usually wise to stop there, unless a primary focus is easily found. It is not usually possible to determine the location of the primary lesion merely by the clinical findings and the local or x-ray examinations. The more common sites are the thyroid gland, lung, stomach and kidneys. Malignant lymphoma is also a possibility. The liver edge was felt; it was rather tender, suggesting that the tumor had also metastasized to the liver. She had pelvic pain, low-back pain and leg pain. I gather that that phase was not investigated much further. Was that the characteristic distribution of pain occurring with involvement of the nerve roots that form the sciatic plexus?

DR. JACOBSON: Yes.

DR. BARR: The pain occurring alone would suggest a prolapsed intervertebral disk, but since it occurred with other organic lesions one wonders if there were metastases to the region of the lower lumbar spine or pelvis. I can only go so far as to say that I believe she had metastatic neoplastic disease involving the third dorsal vertebra. Dr. Wyman has convinced me that the kidney was a factor — and she probably had a metastasis from a renal neoplasm.

DR. WILLIAM H. SWEET: I am a trifle nonplused at Dr. Barr's comments about inserting a needle paravertebrally at the level of the upper thoracic spine. I have put more needles alongside the first three thoracic vertebras than anywhere else along the spinal column. Following the suggestion made by Dr. James C. White ten years ago, we do this under x-ray control, as you see in the films; we have not found it dangerous when the precautions used by Dr. White are followed. I must confess that when I aspirated arterial blood I thought this might have been the occasion Dr. Barr was referring to.

DR. BARR: The remark I made is based on the observations of a South American group, Valls, Ottolenghi and Schajowicz,* who have been much interested in vertebral biopsies and have done extensive anatomic studies. That was almost a direct quotation from their work. Undoubtedly, with careful handling of needles, relatively innocuous exploration can be done anywhere. Neurosurgeons put needles into all sorts of difficult spots and think nothing of it.

CLINICAL DIAGNOSIS

Metastatic carcinoma.

DR. BARR'S DIAGNOSIS

Metastatic carcinoma of vertebra, probably from kidney.

ANATOMICAL DIAGNOSIS

Renal-cell carcinoma, with metastases to spine, ribs, humeri, scapulas, liver and ovaries.

PATHOLOGICAL DISCUSSION

DR. SWEET: At operation a small piece of tissue was removed for frozen section from the epidural mass exposed. When it was reported as metastatic carcinoma, the operation was terminated.

DR. TRACY B. MALLORY: My department is usually notably reluctant to try to name the primary sites of metastatic tumors. However, when we see a papillary adenocarcinoma, which was what the biopsy showed, we think in terms of three organs: kidney, thyroid and ovary — of which the first is prone to metastasize to bone. In this case the clinical record suggested that there was enlargement of the thyroid gland, the x-ray films showed possible evidence of renal involvement and the gynecologist felt a large mass in the pelvis. Because some of the cells were vacuolated, we also suggested the possibility of renal origin. The autopsy performed about four months after the patient was discharged from the hospital left no room for doubt. No tumor was found in the thyroid gland. The primary lesion was a small tumor in the left kidney, limited to the cortex and coming very close to the pelvis but not, as far as I could see, deforming it — so that I do not feel certain that even a retrograde pyelogram would demonstrate it. There were extensive metastases. The liver was full of tumor and there were metastases in the lung and multiple lesions in bone other than the vertebral ones. Eventually both humeri were largely destroyed by pathologic fractures, and examination of the bone marrow showed multiple foci of tumor scattered throughout.

DR. WYMAN: Dr. Richard Chute has just had a case somewhat like this one. The intravenous and retrograde pyelograms were negative. The patient had bleeding from the ureter, and a kidney tumor

*Valls, J., Ottolenghi, C. E., and Schajowicz, F. Aspiration biopsy in diagnosis of lesions of vertebral bodies. *J. A. M. A.* 136:376-382, 1948.

was suspected. We are trying to study the arterial systems in these cases and hope to delineate some of these tumors by so-called nephrography.

DR. MARIAN ROPES: What was the pelvic mass?

DR. MALLORY: There were multiple large ovarian metastases.

CASE 37132

PRESENTATION OF CASE

First admission. A sixty-nine-year-old woman was admitted to the hospital because of sharp epigastric and right-upper-quadrant pain often radiating through to the back, usually occurring after eating, frequently associated with vomiting, chills and fever, never accompanied by the presence of dark urine or clay-colored stools, and never relieved by food or drink. Jaundice was observed by friends about one week before entry. Moderate exertion caused dyspnea and palpitations but seemed unrelated to pain.

Physical examination revealed an obese woman in no acute distress. Clinical evidence of jaundice was absent. The chest was clear to percussion and auscultation; the left cardiac border was 9 cm. from the midsternal line in the fifth intercostal space. A high-pitched Grade III aortic systolic murmur and a Grade II apical systolic murmur were heard; the pulmonic second sound equaled the aortic. The liver edge was questionably palpable, but upper-quadrant tenderness prevented adequate examination.

The temperature was 100°F. and the pulse 68. The blood pressure was 110 systolic, 50 diastolic.

The urine was acid, amber in color, contained no sugar, bile or albumin and had a specific gravity of 1.010; the sediment contained 3 to 4 white cells per high-power field. Examination of the blood revealed a hemoglobin of 13 gm. per 100 cc. The blood Hinton test was negative. The total protein was 7.0 gm., the albumin 4.16 gm., the globulin 2.85 gm. (an albumin-globulin ratio of 1.5), the nonprotein nitrogen 22 mg. and the serum amylase 45 units per 100 cc.; the chloride concentration was 103 milliequiv. per liter. The prothrombin time was 28 seconds (normal, 19 seconds) and the van den Bergh reaction normal. Two stools were guaiac negative. A posteroanterior film of the chest demonstrated clear lung fields with the cardiac shadow lying in a slightly transverse position. The minimally tortuous aorta had calcification in its arch. A gastrointestinal series was negative. Dye was not concentrated in the Graham test.

A laparotomy was performed with removal of the gall bladder, which was markedly thickened and contained a palpable stone. The common duct was normal to palpation and was not explored. The pathological report was acute and chronic cholecystitis. The postoperative course was uneventful.

Final admission (five years later). Two years after operation the patient visited the Out Patient Department complaining of hemoptysis. On examination, bright-red blood was noted on the soft palate. Admission to the Emergency Ward at that time disclosed no change in the chest x-ray findings from a previous film, but the sputum examination demonstrated rare acid-fast bacilli. No site of possible bleeding was seen by the laryngologist. The patient was referred to the Boston City Health Department, where it was decided that there was no active pulmonary disease.

Two weeks prior to entry she reported at the Medical Clinic that she had had an acute episode of nonradiating right-upper-quadrant pain three weeks before that was associated with nausea but not with vomiting, chills or fever. She had felt weak and clammy during the attack. Subsequently the pain persisted as a dull, steady epigastric ache, described as not unlike the discomfort experienced prior to cholecystectomy. There had been progressive weight loss over the past year of at least 15 pounds attributed to omission of fatty foods from the diet. Nine months before admission, while walking or standing in the street, she had had three episodes of unconsciousness without prodromata. Competent witnesses reported no convulsions or tongue biting during these attacks. Orthopnea, pruritus, cough, further hemoptysis or darkening of the urine had not been observed, although constipation was progressively more bothersome, with occasional blood-streaking of dark-brown stools. Physical examination at the clinic showed a blood pressure of 140 systolic, 90 diastolic, a pulse of 68 and respirations of 18. The heart was enlarged to the anterior axillary line. A Grade III high-pitched, blowing systolic murmur, best heard to the right of the sternum in the second intercostal space, was transmitted to the apex, and the aortic second sound was inaudible. The right upper quadrant was tender to palpation, although no masses were felt. Pressure in the lower quadrants caused slight referred pain to the right upper quadrant. Jarring of the right costal margin produced no pain. Although the liver edge was not felt with certainty, it was thought to be 3 fingerbreadths below the costal margin. X-ray films of the chest and abdomen were essentially normal, but a gastrointestinal series made a week later demonstrated multiple irregular rounded defects in the distal esophagus, a small hiatus hernia and normal stomach and duodenum. The patient entered the Emergency Ward complaining that despite straining no stools had been passed since barium administration a week previously, and that her abdomen had increased markedly in size and was now diffusely painful.

Physical examination showed an obese, moderately dehydrated woman who appeared acutely ill. The

heart and lungs were unchanged. The abdomen was tremendously distended, with a nontender liver edge palpable 5 fingerbreadths below the costal margin. A fluid shift was demonstrable. Proctoscopic examination following a negative rectal examination was normal to a distance of 7 cm., where the presence of abundant feces prohibited further observation. Deep reflexes were equal and active bilaterally. There were bilateral plantar flexor responses.

Urinalysis was negative except for a ++ test for albumin. The stool was guaiac negative. Examination of the blood showed a hemoglobin of 14.8 gm. per 100 cc. and a white-cell count of 10,700, with 78 per cent neutrophils. The nonprotein nitrogen was 55 mg., the total protein 5.5 gm. and the van den Bergh reaction 1.7 mg. direct, 2.4 mg. total, per 100 cc.; the chloride was 91 milliequiv., the sodium 120 milliequiv., the carbon dioxide 23.3 milliequiv. per liter and the prothrombin time 57 per cent. A plain film of the abdomen showed no distended loops of bowel.

A Miller–Abbott tube was kept in place for the first twenty-four hours but was removed because very little drainage resulted. This was followed by paracentesis, with removal of 5000 cc. of clear fluid having a specific gravity of 1.015 and containing a few white cells and a moderate number of old crenated red cells. The following day the patient felt very nauseated and appeared much more ill than previously in spite of unaltered blood chemical levels. Twenty-four hours later respirations increased, the temperature was elevated to 100°F., the pulse became weak and the blood pressure fell unaccountably to 82 systolic, 68 diastolic. The patient died on the third hospital day.

Differential Diagnosis

Dr. Daniel S. Ellis*: It seems to me that I have the problem of deciding whether this woman had one or more diseases referable to the following organ systems: the cardiac system, the pulmonary system or the biliary tract. The symptoms during the first admission seem to have been straightforward; I am unable to detect anything other than acute or chronic cholecystitis, with cholelithiasis plus some heart disease that I shall assume was of an arteriosclerotic nature — probably calcific aortic stenosis. It would be nice to know what the liver looked like at the time the gall bladder was taken out. Dr. Mallory, is there any record of that in the operative note?

Dr. Tracy B. Mallory: No mention was made of the appearance of the liver.

Dr. Ellis: It will be safer, then, to assume that it was not examined.

I think I should like to see the x-ray films. Dr. McCort, I should like to know what you see in the chest plate, with regard to the size of the heart and the possible presence of pulmonary disease, that might explain the hemoptysis.

Dr. James J. McCort: The x-ray films of the chest taken on the first admission show clear lung fields and no fluid in either costophrenic sinus. There is no evidence of intrapulmonary disease. The heart is transverse because the patient is rather obese, and there is a suggestion of enlargement of the left ventricle. The aorta is elongated and slightly tortuous and shows a ring of calcification in its arch. The gastrointestinal series made on the first admission disclosed a normal stomach and duodenum. The round calcification in the right upper quadrant may be the gallstone found at the subsequent operation. A Graham test at the time of the first admission demonstrates poor concentration of the dye. A film of the chest taken two years later during the time she had hemoptysis shows no change from the initial examination and no cause for the hemoptysis.

Dr. Ellis: Did she have an x-ray examination on the last admission?

Dr. McCort: The films of the chest taken on the last admission again show clear lung fields. There has been no appreciable change in the contour of the aorta; it may be slightly elongated. No intracardiac calcification is seen on the film and none was reported on fluoroscopy. There is again no evidence of intrapulmonary disease. The plain film of the abdomen made at the same time fails to reveal any evidence of small- or large-bowel dilatation. The kidneys do not appear to be enlarged. There are no abnormal intra-abdominal calcifications.

Dr. Ellis: Does the esophagus show varices, or are these round nodules tumor?

Dr. McCort: The gastrointestinal tract was examined during the last admission. The swallowing function was normal and the esophagus was not dilated. On the film is seen a nodularity of the lower end of the esophagus, which I would interpret as being due to muscular contractions of the esophagus, forming transverse folds in the mucous membrane. The mechanism of this phenomenon is not clearly understood and it has no known pathologic significance. Many names have been applied to this appearance. The one most commonly used is that suggested by Schatzki† in 1933, who called it "Kräuselung" or "curling." With "curling" the esophagus is not dilated and the folds in the mucous membrane are more or less transverse; with varices the esophagus tends to be dilated and the folds diagonal or longitudinal. There is no abnormality demonstrated in the gastrointestinal tract except for a small and probably insignificant hiatus hernia. The stomach is high and transverse in position. There is no deformity of the duodenal loop.

Dr. Ellis: You do think that loop is large?

*Assistant physician, Massachusetts General Hospital.

†Schatzki, R. Reliefstudien an der normalen und Krankhaft veränderten Speiseröhre. *Acta radiol.* Supp. 18; 1-149, 1933.

DR. MCCORT: The wide loop appears to be the result of the high, transverse stomach in an obese person. The last examination of the abdomen was made one week after the gastrointestinal series. It somewhat belies the statement that she had had no bowel movement, because the greater portion of the barium has left the intestinal tract except for a trace well down in the sigmoid and rectum. There is now a homogeneous increase in density of the entire abdomen, particularly in the pelvis, with the loss of the properitoneal fat lines. A few slightly dilated loops of small bowel are present in the mid-abdomen. There is very little gas or feces in the colon. The stomach is seen to be high and transverse. There is no air in the biliary tree and no air free in the peritoneal cavity. The changes at this time indicate increased intraperitoneal fluid.

DR. ELLIS: The x-ray findings disappoint me because I am forced to agree with you that the deformity of the esophagus looks like curling rather than varices and I had expected an abnormality in the form of varices to explain the hemoptysis.

I still have to explain the occurrence of severe pain, which was described as similar to the pain before the gall bladder was removed; the queer attacks of loss of consciousness that were not convulsive seizures; the blood chemical levels, namely a low chloride and low sodium; and the hemoptysis. The more I try to explain all of these, the more confused I become.

I shall take the heart to begin with, and see if there is any chance of the whole picture's being explained by the heart disease. If the patient had arteriosclerotic heart disease with calcific aortic stenosis, then the attacks of syncope and loss of consciousness may possibly have been due to a Stokes-Adams syndrome or to some transitory cerebral anoxia. I cannot rule that out. I shall say it is a possibility. Is there any question that she had congestive failure that might explain the ascites and big liver? It definitely was not tender. There was no history of peripheral edema, so that I have to look elsewhere for the explanation of the ascites and hepatomegaly. Could the pain by any chance have been related to the heart disease? Could the episode of hypotension be related to myocardial infarction? Is there any chance that she had a dissecting aneurysm? Could the terminal episode have been one of bleeding into an organ, other than the gut, that was not recognized? They are all possible, but I cannot find anything in the protocol to make me want to hang my hat on any of those diagnoses. I am going to say that the heart was as stated, that there was no congestive failure, that the heart condition played no part in the ascites and hepatomegaly and that the attacks of syncope may or may not have been due to cerebral anoxia as a result of heart disease.

Did this patient have tuberculosis? Usually a positive sputum is proof that a patient has tuberculosis. Yet there was nothing in the chest plates, and nothing occurred in the subsequent two years after this was suspected to give me any clues. Is it possible that she had unrecognized pulmonary tuberculosis with tuberculosis involving the adrenal glands, the peritoneum and possibly the liver to account for the picture? Yes; it is quite possible. There may have been some element of adrenal insufficiency to account for the change in blood chemical findings, for the hypotension on one occasion and perhaps for some transitory hypoglycemia, but I cannot believe that this was the whole explanation. Certainly there was nothing but the one sputum to suggest that she had pulmonary tuberculosis. She may have had visceral tuberculosis elsewhere. I shall leave that for the moment.

What about the possibility of her having a common-duct stone over all these years and developing a biliary cirrhosis? The epigastric pain could have been due to a common-duct stone that had not caused complete obstruction and therefore did not cause jaundice but had caused enough relative obstruction to lead to liver impairment and biliary cirrhosis with varices, ascites, hepatomegaly and a low prothrombin time. I think that if she had a common-duct stone that was causing enough relative obstruction to lead to that picture as a terminal event, she almost certainly would have had jaundice from time to time, the spleen would have been large enough to feel and the liver enlargement would not have been quite so sudden as that described in the history. I should like to know what the alkaline phosphatase or the cephalin-flocculation test showed but I assume they were not done. The only laboratory finding that suggests liver disease was the low prothrombin time.

Among other possibilities is the question whether or not there was a malignant process. If so, I could explain the loss of weight on that basis. If the patient had metastatic cancer involving the liver, that would explain the enlarged liver and possibly the low prothrombin time. An alkaline phosphatase determination would be most helpful. Varices are not very common solely on the basis of cancer of the liver without obstruction to the portal system; besides, the x-ray films do not bear out the presence of varices. Were the adrenal glands involved with metastatic disease? The most common sources of metastases to the adrenal gland are the breast and the lung, and there was nothing to indicate a malignant process in either of these organs. Where may a primary lesion have been? The story of increasing constipation, of blood-streaking in the stools and of some obstipation before she was admitted are all very enticing suggestions that she had a cancer in the colon above the part that was investigated by the sigmoidoscope. If she had a lesion there that caused that much obstipation, I should think there would have been some evi-

dence of dilatation and gas in the proximal bowel that was not present.

These are the possibilities as I see them. I think there are some things that I am going to have to leave unexplained. I think the condition that would fit the picture best and explain most of the findings (in addition to the heart disease that I have already mentioned) is malignant disease involving the liver. That would account for the increased size of the liver without evidence of more impairment of liver function. The best clue I have points to the colon, so that I shall pick as my first diagnosis carcinoma of the colon with metastases to the liver. I cannot rule out carcinoma of the head of the pancreas with metastases — and her pain is more suggestive of that. I wonder also whether this might be the rare patient who has tuberculosis of the liver and peritoneum, and ascites with an enlarging liver on that basis. I shall make that my second choice.

Dr. Arthur S. Pier: Would you consider a carcinoma of the ovary with this ascites, Dr. Ellis?

Dr. Ellis: I do not know how often carcinoma of the ovary metastasizes to the liver. Perhaps Dr. Mallory can tell us. The most common sources of metastatic disease in the liver are the rectum and colon and then the pancreas.

Dr. Mallory: The ovary would be relatively uncommon.

Dr. George L. Nardi: The onset of ascites was relatively rapid. Because of the scar on the abdomen, the abdominal pain and failure to pass gas and feces, we believed that the patient had intestinal obstruction. Since she had a history of having received barium and since we have just seen a case of perforation due to barium impaction we were sensitized to that possibility. We ordered x-ray films, with a diagnosis of intestinal obstruction, and then we had to explain failure of x-ray confirmation. We examined her again and found shifting dullness and an enlarged liver. When we tapped her we obtained clear straw-colored fluid.

Dr. Ellis: The presence of the crenated red cells influenced me to make malignant disease my first choice. Crenated red cells are not found in the ascitic fluid on any other basis that I can think of.

Clinical Diagnoses

Cirrhosis of liver with ascites.
Aortic stenosis.

Dr. Ellis's Diagnoses

Metastatic carcinoma of liver and peritoneum from colon or pancreas.
Arteriosclerotic heart disease with calcific aortic stenosis.

Anatomical Diagnoses

Adenocarcinoma of body and tail of the pancreas with metastases to liver, peritoneum and lymph nodes.

Calcareous aortic stenosis.

Pathological Discussion

Dr. Mallory: The autopsy showed that this patient had, as Dr. Ellis predicted, an abnormal heart with involvement of the aortic valve. The cusps were thickened, interadherent and slightly calcareous. It did not seem like a very severe lesion. The hypertrophy of the heart was relatively slight — it weighed only 450 gm. — and she was a big, obese woman. There was no severe degree of passive congestion in the lungs or liver, so that we did not think that heart failure was the cause of death.

The major finding at autopsy was a tumor that occupied the body and tail of the pancreas and was quite obviously carcinoma. This had metastasized to the regional lymph nodes and rather extensively to the liver. The liver was not extremely large — it weighed only 1350 gm., which is within normal limits of weight, but there were a great many minute metastases. One possibility that should be considered would be that the syncope was on a hypoglycemic basis, but the pancreatic tumor was an adenocarcinoma composed of mucin-producing cells and definitely not an islet-cell tumor, so that I think this is ruled out. We were unable to find any tuberculosis and there was certainly none in the lungs to explain the positive sputum.

Dr. Ellis: Did she have any metastases to the brain or the adrenal gland?

Dr. Mallory: None were present.

Dr. Ellis: Dr. Bland, do you think the syncope was due to the heart disease?

Dr. Edward F. Bland: No; I do not think she had enough heart disease to account for that. Now I am going to ask you to explain the chemical findings.

Dr. Ellis: I do not have any reasonable explanation for them. Judging from the history, she was not vomiting enough to account for them. Perhaps Dr. Mallory will reveal some renal disease that would explain them, but I cannot answer your question.

Dr. Mallory: The kidneys appeared normal.

Dr. Currens: She probably lost a fair amount of sodium and chloride into the abdomen. The ascites was relatively sudden in onset.

Dr. Ellis: Dr. Nardi says she was on Miller-Abbott suction. Even so, the electrolyte values are pretty low. One does not usually see such figures unless the patient is severely dehydrated.

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†Representing the New Hampshire Medical Society.

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MONEY TALKS

The *Journal*, according to a most solemn and infrangible rule of the Council of the Massachusetts Medical Society, is mailed with the greatest possible fidelity to all fellows of the Society whose annual dues are paid up to date on the first day of March of any current year. Some 20,000 additional subscribers are willing — nay, eager — to pay a modest extra premium for the privilege of receiving the *Journal*, but that is neither here nor there.

It is a further requirement of the Council that after the Kalends of March the names of delinquent fellows shall be removed from the mailing list. In 1949, 785 fellows were thus deprived of one issue or more of the *Journal*; in 1950, 651 forgot to mail the check; last week 1370 doorbells failed to feel the pressure of the postman's finger.

Moreover, like tomatoes that the frost has nipped, these last numbers can never be retrieved; the printing order is dependent each week on the anticipated circulation. The only balm in this particular Gilead is the saving that accrues to the *Journal* from not distributing copies at less than half their cost, which is what the fellows of the Society pay for these priceless specimens of contemporary medical literature; it is like being paid for not planting corn.

This is, however, a shallow recompense to the editors, who believe that their true destiny lies in the dissemination of knowledge as widely as possible, not in pinching pennies of steadily decreasing value. "Who steals my purse," and so forth.

One is reminded, of course, of the minister who denounces the constant part of his congregation for the backslidings of the rest, and one becomes again conscious of the reputation being developed by a minority of the organized profession of Massachusetts (there she stands!) for nonpayment of dues.

Since only the faithful 80 per cent will receive this issue of the *Journal*, it is requested that they remind the recalcitrant 20 of the reason for its nonappearance in those other letter slots.

BOARD OF CLINICAL CHEMISTRY

In view of the generally salutary effect of the specialty boards on medical practice, the recent establishment and incorporation of an American Board of Clinical Chemistry must be greeted with satisfaction and approval. This new certifying board has been organized under the auspices of the American Chemical Society, Inc., the American Institute of Chemists, Inc., and the American Society of Biological Chemists, Inc. Its purpose is:

> to encourage the study, improve the practice, elevate and establish standards and advance the science of that specialized branch of chemistry entitled "clinical chemistry"; to grant and issue certificates or other recognition of special knowledge in clinical chemistry to voluntary applicants who in accordance with the by-laws, rules and regulations of the Board have established their fitness and competence; to prepare and furnish in the public interest a registry of individuals with specialized knowledge in clinical chemistry who have from time to time been granted certificates by the Board.

Despite the petulant animadversions with which any reference to the specialty boards is occasionally

greeted in certain quarters, these certifying panels have nevertheless been of incalculable value in establishing and maintaining improved standards of medical practice. That toes have been stepped on goes without saying, and if a faint odor of sanctity occasionally steals from behind the paneled doors, it may be considered only an attempt to conceal the ordinarily forthright qualities of human nature. If the boards have sometimes overshot their mark and momentarily lost sight of the universal goal in medicine of delivering the greatest good to the greatest number, the lapse may be attributed merely to an overabundance of zeal.

The new board, devoted to the attainment of excellence in a relatively exact science, may be expected to add prestige to all such regulatory apparatus.

GÖSTA FORSSELL

Professor Gösta Forssell, recognized throughout the world as a pioneer in radiology, died on November 13, 1950, in his native Sweden.

Dr. Forssell's interest in radiology dated back to his student days; he was still a young man when, in 1906, he established the X-ray Department at the Serafimer Hospital, in Stockholm, which he headed until his retirement in 1940. He was a leader in founding, in 1910, the Radiumhemmet, which became one of the leading radiotherapeutic centers of the world. He held the post of professor of radiology at the Royal Caroline Hospital and Institute from 1917 to 1941 and was influential in the establishment of similar professorships in Sweden. Universally respected as a great teacher and organizer of teaching and research programs in both radiology and medicine, he was in 1928 invested with the presidency of the Swedish National Foundation for the treatment of cancer, under the King Gustav Fund.

Dr. Forssell will be most generally remembered in this country as the founder and editor of the *Acta radiologica*. This publication has reached its thirty-third volume, together with seventy-seven supplementary monographs on special subjects. It was through this medium of world-wide influence that he, his pupils and his colleagues made some of the most valuable contributions to medical, scientific and radiologic knowledge.

THE MARCH OF TIME

The obituary of Amy Florence Wakley, who died in her ninety-fifth year on November 14, 1950, appeared in *The Lancet* of November 25. This notice, unobtrusive though it was, must nevertheless have excited some interest in British medical circles, for Miss Wakley was the granddaughter of Thomas Wakley, who was born in 1795, founded *The Lancet* in 1823 and was its editor from then until 1862. Three generations of Wakleys thus spanned a century and a half and more, giving rise to *The Lancet's* comment that "This hardy strain, deriving from Devon farmers, inherits the vitality which made Thomas Wakley an outstanding character."

The occasional overlapping of long lives was interestingly illustrated on April 19, 1950. On that anniversary, a hundred and seventy-five years after the event, Dr. Alfred Worcester, of Waltham, then also in his ninety-fifth year, broadcast an eyewitness account of the battle of Lexington that had been related to him when he was five years old by his great-grandmother, his senior by ninety years, who had observed parts of the famous action.

Remuneration of Medical Attendants in France. — . . . *we find that the majority of medical men . . . are lamentably paid, the principal cause of this sad state of things being the unfortunate practice of underselling one another. There are surgeons in the country who will pay a visit for five pence, and even two pence half-penny; attend a midwifery case for twenty pence or half a crown; set a limb for ten pence, &c. &c.*

Boston M. & S. J., *April 2, 1851*

MASSACHUSETTS MEDICAL SOCIETY

DEATH

White — Michael W. White, M.D., of Somerville, died on January 1. He was in his seventy-ninth year.

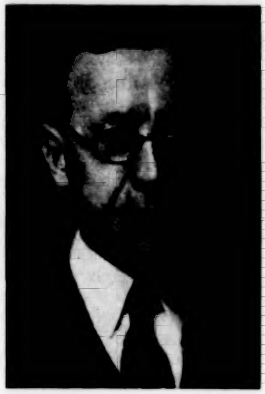
Dr. White received his degree from Harvard Medical School in 1898. He was a fellow of the American Medical Association.

Two daughters, a son, a brother, a sister and a nephew survive.

NEW HAMPSHIRE MEDICAL SOCIETY

DR. ROBERT J. GRAVES

1878-1950



Dr. Robert John Graves was born on June 22, 1878, in Boscawen, New Hampshire, the son of Eli Edwin Graves and Martha (Williams) Graves. He died on July 12, 1950.

Dr. Graves attended Concord High School. He graduated from Harvard University in 1900 and from Harvard Medical School in 1903.

After internship at the Massachusetts General and Boston Lying-in hospitals, he began the practice of general surgery in Concord, where he practiced until his retirement in 1948. He studied abroad in 1914 and was a major in the Army Medical Corps in World War I, serving as chief of the orthopedic service at Fort McHenry. He was chief surgeon of the Boston and Maine Railroad, a former president of the New Hampshire Medical Society, medical director of the United Life and Accident Company and a fellow of the American College of Surgeons and other professional societies.

Dr. Graves was a past vice-president of the American Iris Society, past president of the Concord Rotary club and past commander of Concord Post, American Legion. He also held membership in Eureka Lodge, F. and A. M., and White Mountain Lodge, I.O.O.F.

In 1942 he moved to Hopkinton, where he continued his hobby of iris hybridizing. He was voted the Dykes Medal, the highest award of the American Iris Society, for his beautiful blue Helen McGregor, in 1950.

Survivors include his wife, Mrs. Helen Ayers Graves; a son, John J. Graves, of Hopkinton; three daughters, Mrs. Katherine Larmon, of Hanover, Mrs. Jane G. Howard, of Concord, and Mrs. Robin M. Koch, of Katonah, New York; a sister, Mrs. Katherine G. Rolfe, of Penacook; and nine grandchildren.

R. W. T.

PRIZE ESSAY, 1951

Nearly 100 junior and senior high-school students in New Hampshire public, private and parochial schools have indicated an interest in the Medical Society's 1951 essay contest. The winner of the contest will receive $25. The second prize is $10 and there will be three $5 awards for winners of the third fourth and fifth prizes. The contest closed March 1.

CIVIL DEFENSE APPOINTMENTS

Dr. James W. Jameson, of Concord, New Hampshire Medical Society trustee, has been named Director of Emergency Physician Services. Dr. Joseph M. McCarthy, also of Concord, is assistant director.

These appointments were made by Rear Admiral Miles Browning, U.S.N. (ret.), after a meeting of the Society's House of Delegates on January 28, when a plan of co-ordination between the Society's Emergency Medical Service Committee and the State Civil Defense Organization was approved.

BUDGET FOR 1951

A 1951 budget of $23,000 was voted by the New Hampshire Medical Society's House of Delegates at a special session on January 28. The new budget, well below 1950 expenditures, will necessitate some curtailment in Society service and activities but provides funds for continuation of the executive office and a more conservative public-relations effort.

The Society's 1951 budget earmarks $2875 for payment to the reserve fund and some $2000 for the contingency fund. Slightly more than half the budget allocation will go toward salaries and expenses of officers, delegates and committees.

The 1951 budget for printing has been reduced to $810. This will provide for a four-page quarterly publication. One thousand dollars has been budgeted for the 1950 Transactions, with a similar amount for the Society's Benevolence Fund.

The Society expects to receive some $20,000 of its estimated $23,000 income from 1951 dues of $40, which are payable to the individual county medical society treasurers. Some profit is anticipated from the 1951 annual meeting, which will be combined with the Vermont State Medical Society and held at the Equinox House, Manchester, Vermont, on September 30, October 1 and 2.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

FIELD TRAINING FOR PUBLIC-HEALTH PERSONNEL

Massachusetts can claim another "first" in the field of progressive public-health practice. The American Medical Association has approved a specialty board in Preventive Medicine and Public Health, and Massachusetts has been selected as one of the ten states in which the supervised field-training portion of accredited residency may be taken by qualified physicians.

Field training is not something separate from, or a competitor of, academic instruction, but rather supplements and complements classroom and laboratory instruction. Field training is to public-health education what the internship is to medical education. Residency programs must be sufficiently broad in scope to equip the trainee with the basic knowledge necessary for appropriate action whenever and wherever he may be confronted with the various public-health problems originating in a community.

Great variation exists in the forms and objectives of field training, and although the purposes of the various types are different they all have a place in the educational development of health-department personnel. Programs vary from short periods of observation, usually measured in days, to one-year residencies, including all the training activities and functions referred to as observation, orientation, apprenticeship and supervised field experience.

The Department has recently received a grant, totaling $141,712, from the W. K. Kellogg Foundation to assist in developing field-training facilities in Massachusetts for health officers, nurses, sanitary engineers, sanitarians, health educators and administrative assistants. This grant permits the Department to enlarge its previously established training activities, which in addition to a variety of in-service programs also include a more formal program of field training of medical social workers and sanitation personnel.

Dr. Leon A. Bradley has been appointed director of the Field Training Program and the following staff will supervise instruction under the various categories: health officers, Dr. Roy F. Feemster; nurses, Miss Mary E. Chayer; sanitation personnel, Mr. Earl J. Anderson; medical social workers, Mrs. Esther Spencer.

An advisory committee on training has already held a meeting for organization and preliminary planning of administrative policy. The personnel of this committee includes Dr. Hugh Leavell, Dr. Fred Mayes, Professor Curtis M. Hilliard, Miss Mary Maher, Mr. Peter Karalekas, Mr. John F. Smith, Miss Elizabeth Rice, Dr. Helen Roberts and Mrs. Mary Carr Baker.

The field-training programs for sanitation personnel and medical social workers are now functioning, and in the near future supervised field training for nurses and residencies for physicians will be developed sufficiently to permit the acceptance of trainees.

EPIDEMIOLOGIC ASPECTS OF CANCER OF THE CERVIX

Statistical studies relating to the etiology of cancer have been a major activity of the Massachusetts Department of Public Health since the inception of its cancer-control program in 1926. One of the earlier studies showed a correlation between cancer and nativity. To determine the reasons for this, studies on the relation of cancer of different sites to heredity and environmental factors seemed advisable.

Two recent reports of a study of factors associated with cancer of the cervix were published in 1950, the first in *Revue acta* and the second in the journal *Cancer*. The study consisted of a comparison of the environmental factors among persons with and without cancer, to determine the possible etiology of this disease.

The questionnaire sought information on diet, manner of eating, habits of elimination, clothing, previous diseases, possible endocrinologic abnormalities, nativity, economic status, familial history of cancer and other chronic diseases, catamenia, pregnancies and certain marital habits.

The most important findings were connected with the marital status. A relation between early marriage and cancer of the cervix was shown, since 44.6 per cent of the women with cancer of the cervix were married before the age of 20, as contrasted with 23.7 per cent of the matched controls.

Among the cervical cancer group 20.7 per cent of the women were divorced or separated at one time or another, as contrasted with 6.7 per cent in the control group.

The relation between unrepaired laceratoins and cancer of the cervix was strong. Of the subjects with cancer of the cervix, 26 per cent were found to have lacerations, as compared with 13.2 per cent of the controls.

The cessation of birth of children before the mother had reached the age of 25 occurred to a significantly greater extent among those with cancer of the cervix.

An association between cancer of the cervix and syphilis has been reported by several investigators and confirmed in this study.

There was evidence to suggest that more cervical cancer could be found among the poor than among those in moderate and comfortable circumstances.

The reasons for the various correlations are not clear, although there is a suspicion that infections, chronic irritation and hormonal imbalance are of considerable importance.

HERBERT L. LOMBARD, M.D.

MISCELLANY

MILITARY INTERN PROGRAM

The appointment of 132 senior medical students for the military intern program of the Army Medical Service has been announced by Major General R. W. Bliss, Army Surgeon General. This program provides that medical students may, upon graduation, be commissioned in the Medical Corps Reserve and serve their internship in an Army hospital with the pay and allowance of a first lieutenant. For the first time since World War II there is now a requirement that the new doctors serve one year on active duty in addition to their year of internship.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Progress in Neurology and Psychiatry: An annual review. Vol. V. Edited by E. A. Spiegel, M.D., professor and head of the Department of Experimental Neurology, Temple University School of Medicine, Philadelphia, Pennsylvania. 8°, cloth, 621 pp. New York: Grune and Stratton, 1950. $10.

Volume Five of this important progress report is the joint work of 64 contributors who have surveyed the literature for the last part of 1948 and for 1949. The text is divided into four parts: the basic sciences, neurology, neurosurgery and psychiatry. Lists of references are appended to the chapters. The book is well published, and the set should be in all medical libraries and available to neurologists and psychiatrists.

Love is Not Enough: The treatment of emotionally disturbed children. By Bruno Bettelheim. 8°, cloth, 386 pp., with 16 plates. Glencoe, Illinois: Free Press, 1950. $4.50.

Mr. Bettelheim describes the work of the University of Chicago Sonia Shankman Orthogenic School. It is an experimental or laboratory residential school for children six to fourteen years of age who are physically fit and of normal or better than normal intelligence but who suffer from severe emotional disturbances that have failed to respond to all previous efforts at treatment. The disturbances range all the way from delinquency and functional inability to read to "childhood schizophrenia." The children remain in the school for two or three years on the average. Mass psychoanalysis is practiced on a twenty-four-hour basis. The staff of the school, all specialists in their particular fields, convince the children that this world can be a good one to live in by helping them to succeed in the simple tasks of living that have somehow become difficult for them and always ended in defeat because of environmental conditions. The children are always under treatment, passive or active, from the time they get up in the morning until they go to bed at night. The school has been successful in rehabilitating this type of child. The book is well published and has a good index. It should be found in all collections on psychiatry and psychoanalysis.

The Physiology of Tissues and Organs: An introduction to the study of systematic physiology. By Douglas H. K. Lee, M.D., M.Sc., D.T.M., professor of physiological climatology, Johns Hopkins University School of Medicine. 8°, cloth, 159 pp., with 30 illustrations. Springfield, Illinois: Charles C Thomas, 1950. $4.

This book was first published by the University of Queensland and was received so well by the professional public that it has been issued in an American edition. It is intended as a student's textbook but may well be read by other persons interested in the subject. The text is divided into two main parts: the physiology of tissues and the physiology of organs. The first part considers the basic processes of living matter and deals with the behavior and chemical and physical changes of living cells and discusses specific cells. An attempt is made to show that all tissues possess to varying degrees the fundamental functions of living cells. There is a special chapter on the aging of tissues. The second part deals with the various organs of the body, grouped in a classification according to their functions. There are special chapters on the organs of defense and offense, and on the embryo as an organ. The relations between structure and function and the specific purpose of an organ are emphasized.

The Causes of Blindness in England and Wales. By Arnold Sorsby. 8°, paper, 42 pp., with 7 tables. London: His Majesty's Stationery Office, 1950. 1s. 6d. net. (Medical Research Council Memorandum No. 24.)

The author made a comprehensive survey in England and Wales and found that the present rate of blindness is 21.3 per 100,000 and applies to a group in which 67.6 per cent of the patients are blinded by congenital and hereditary anomalies, including myopia. It is assumed that if the residual 32.4 per cent of cases not due to congenital and hereditary conditions can be eliminated the rate will drop to as low as 15 per 100,000 in the foreseeable future. Beyond that there does not seem to be any likelihood of further decline.

Techniques in British Surgery. Edited by Rodney Maingot, F.R.C.S. 8°, cloth, 733 pp., with 473 illustrations. Philadelphia: W. B. Saunders Company, 1950. $15.

This book on operative surgery presents the technics of surgery in Great Britain. The work is the joint effort of 29 specialists. The text is divided into four main parts: head, neck and spinal column; thorax; abdomen and pelvis; and extremities. There are indexes of authors and subjects. The volume should be in all collections on surgery.

Letters of Jean De Carro to Alexandre Marcet, 1794–1817. Edited with an introduction and notes by Henry E. Sigerist, M.D. 4°, paper, 78 pp. Baltimore: Johns Hopkins Press, 1950. $2. (Supplements to the *Bulletin of the History of Medicine.*)

Dr. De Carro was the first physician to introduce vaccination into Continental Europe soon after its discovery by William Jenner. The twenty-two letters from the Henry Barton Jacobs collection on vaccination in the Welch Medical Library in Baltimore constitute an important part of the history of vaccination, and this small book should be in all collections on the subject and on medical history.

Form- und Wachstumsgesetze drüsenbildender Karzinome. By Professor Dr. Richard Böhmig, superintendent, Pathologisch-Bakteriologischen Instituts der Städtischen Krankenanstalten, Karlsruhe. 8°, paper, 105 pp., with 23 illustrations. Stuttgart: Georg Thieme, 1950. DM 14.-/$3.35. (Distributed by Grune and Stratton, New York.)

This monograph is devoted to the history of the morphology of tumors and discusses the theories of Eugen Albrecht, Martin Heidenhain and Hans Spemann. A bibliography ends the text, and the publishing is excellent. A detailed table of contents takes the place of an index. The monograph should be in all collections on tumors.

NOTICES

ANNOUNCEMENT

Dr. Allen I. Sherman announces the removal of his office to 1019 Centre Street, Newton Centre.

BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

A meeting of the House Officers' Association will be held in the Cheever Auditorium, Boston City Hospital, on Tuesday, April 3, at 7:00 p.m. Dr. Isadore Snapper will speak on the subject "Metabolic Bone Diseases."

NEW ENGLAND HOSPITAL

The monthly clinical conference and meeting of the staff of the New England Hospital will be held in the conference room of the hospital on Thursday, April 5, at 7:15 p.m. Drs.

Olive Smith, Marjorie Woodman and John R. Barker will discuss the subject "Newer Aspects of Hormone Prevention of Miscarriage." Dr. Annella Brown will be chairman.

The meeting will be held under the direction of the Obstetrical Department.

BOSTON SURGICAL SOCIETY

The Boston Surgical Society will award the Henry Jacob Bigelow Medal to Dr. Evarts A. Graham of St. Louis, Missouri, on Friday, April 20, at New England Mutual Hall. Dr. Graham is Bixby Professor of Surgery at Washington University and surgeon-in-chief at Barnes Hospital and St. Louis Children's Hospital.

The Bigelow Medal is an award for new and valuable work in surgery or connected with it. In the past thirty years it has been awarded upon only eleven occasions, Dr. Elliott C. Cutler having been the last recipient, in June, 1947.

MASSACHUSETTS ASSOCIATION OF MEDICAL TECHNOLOGISTS

The second annual meeting of the Massachusetts Association of Medical Technologists will be held at the Museum of Fine Arts, Springfield, on April 21. The following program will be offered:

9:00 a.m. Registration.
9:30 a.m. Business meeting.
11:00 a.m. Some of the Newer Concepts of Surgical Disorders of the Chest. Frederick A. Post, M.D.
12:30 p.m. Luncheon at Christ Church Cathedral Dining Room.
2:00 p.m. Practical Laboratory Aids in the Diagnosis of Parasitic Diseases. William Kaufmann, M.D. Blood-Volume Studies. Louis Hastings, M.D.

All persons interested in the field of medical technology are invited to attend.

AMERICAN COLLEGE OF CHEST PHYSICIANS

The seventeenth annual meeting of the American College of Chest Physicians will be held at the Ambassador Hotel, Atlantic City, New Jersey, June 7-10. An interesting scientific program has been arranged for presentation at the meeting.

The next oral and written examinations for fellowship will be held in Atlantic City on June 7. Candidates who would like to take the examinations for fellowship should contact the executive secretary, American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Illinois.

SOCIETY MEETINGS AND CONFERENCES

April 3. Boston City Hospital House Officers' Association. Page 493.

April 4. Massachusetts Academy of General Practice. Page 458, issue of March 22.

April 4. New England Pediatric Society. Page 346, issue of March 1.

April 5. New England Hospital. Page 493.

April 7. Massachusetts Society of Anesthesiologists. Page 346, issue of March 1.

April 7–28. Springfield Hospital. Page 421, issue of March 15.

April 9–13. American College of Physicians. Page 296, issue of June 15.

April 10. New England Society of Anesthesiologists. Page 512, issue of September 28.

April 10. Harvard Medical Society. Page 457, issue of March 22.

April 11. Tufts Medical Alumni Association. Page 422, issue of March 15.

April 12. The Diagnosis and Treatment of Kidney Diseases in Childhood. Dr. Charles A. Janeway. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

April 18. Physical Medicine and Rehabilitation in Psychiatry. Dr. Walter E. Barton. New England Society of Physical Medicine. Hotel Kenmore. 8 p.m.

April 20. Niles Memorial Lecture. Page 458, issue of March 22.

April 20. Boston Surgical Society. Notice above.

April 21. Massachusetts Association of Medical Technologists. Notice above.

April 24. Norfolk District Medical Society. Page 629, issue of October 19.

April 28. American Psychosomatic Society. Page 198, issue of February 1.

April 28. Alumni Association, Long Island College of Medicine. Page 458, issue of March 22.

May 7–11. National League of Nursing Education. Page 384, issue of March 8.

May 8. New England Society of Anesthesiologists. Page 512, issue of September 28.

May 9. Norfolk District Medical Society. Page 629, issue of October 19.

May 16. New England Obstetrical and Gynecological Society. Hillcrest Country Club, Leicester, Massachusetts.

May 16–18. American Association of Genito-Urinary Surgeons. Page 160, issue of January 25.

May 21–25. International Society of Orthopaedic and Traumatic Surgery. Page 422, issue of March 15.

May 22–24. Massachusetts Medical Society. Annual meeting. Hotel Statler, Boston.

May 24–26. American Goiter Association. Page 384, issue of March 8.

June 7–10. American College of Chest Physicians. Notice above.

June 9 and 10. American Society for the Study of Sterility. Page 274, issue of February 15.

June 11–15. American Medical Association. Annual Session. Atlantic City, New Jersey.

June 15–17. American Electroencephalographic Society. Page 346, issue of March 1.

June 20–23. American Orthopaedic Association. Page 422, issue of March 15.

September 4–8. American Congress of Physical Medicine. Page 238, issue of February 8.

September 19. American Medical Writers' Association. Page 1066, issue of December 28.

September 19–21. Mississippi Valley Medical Society. Page 1066, issue of December 28.

October 31. New England Obstetrical and Gynecological Society. Hotel Somerset, Boston.

November 10–21. Pan-Pacific Surgical Association. Page 680, issue of October 26.

July 8–11, 1952. Thirteenth British Congress of Obstetrics and Gynaecology. Page xv, issue of December 14.

District Medical Societies

HAMPSHIRE

May 2. 4:30 p.m. Annual meeting. Jones Library, Amherst.

NORFOLK

April 24. Boston Medical Library. 8 Fenway. 8:00 p.m.

May 9. Annual dinner.

Calendar of Boston District for the Week Beginning Thursday, April 5

Thursday, April 5

*9:00–10:00 a.m. Grand rounds. Robert Breck Brigham Hospital.
*9:00–10:00 a.m. Cardiac Grand Rounds. Main Amphitheater, Children's Medical Center.
*9:00–11:00 a.m. Medical grand rounds. Joseph H. Pratt Diagnostic Hospital.
7:15 p.m. Clinical conference and staff meeting. New England Hospital.

Friday, April 6

*9:00–10:00 a.m. Medical conference. Joseph H. Pratt Diagnostic Hospital.
*9:00 a.m.–12:00 m. Combined medical and surgical staff rounds. Peter Bent Brigham Hospital.
*10:00 a.m. Surgical clinic. South End Health Unit, 57 East Concord Street, Boston.
*1:30 p.m. Tumor clinic. Outpatient Department, Mount Auburn Hospital, Cambridge.

Saturday, April 7

*9:00–10:00 a.m. Surgical grand rounds. Joseph H. Pratt Diagnostic Hospital.

Monday, April 9

*11:30 a.m.–12:15 p.m. Clinical conference. South End Health Unit, 57 East Concord Street, Boston. Dr. Cleaveland Floyd in charge.
*12:15–1:15 p.m. Clinicopathological conference. Main Amphitheater, Peter Bent Brigham Hospital.

Tuesday, April 10

*9:00–10:00 a.m. Medical conference. Joseph H. Pratt Diagnostic Hospital.
*12:15–1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.
*1:30–2:30 p.m. Pediatric rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

Wednesday, April 11

*9:00–10:00 a.m. Medical conference. Joseph H. Pratt Diagnostic Hospital.
*11:00 a.m.–12:00 m. Medical clinic, including psychiatric conferences. (Children's Medical Center.) Amphitheater, Children's Hospital.
*12:00 m. Clinicopathological conference. Margaret Jewett Hall, Mount Auburn Hospital, Cambridge.
*12:00 m.–1:00 p.m. Clinicopathological conference. (Children's Medical Center.) Amphitheater, Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Combined clinic of all services. (Children's Medical Center.) Amphitheater, Children's Hospital.

*Open to the medical profession.